APL-A-012-13 (NTC02100657)

A Phase I Study of Plitidepsin (Aplidin®) in combination with Bortezomib and Dexamethasone in Patients with Relapsed and/or Refractory Multiple Myeloma

STATISTICAL ANALYSIS PLAN

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-Confidential-

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ABBREVIATIONS AND GLOSSARY

AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
ASCT	Autologous Stem Cell Transplantation
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BL	Baseline
BM	Bone Marrow
BSA	Body Surface Area
CI	Confidence Interval
CPK	Creatine Phosphokinase
CPK-MB	Serum CPK Isoenzymes (Found In Cardiac Muscle)
CR	Complete Remission
CRF	Case Report Form
CT	Chemotherapy
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DB	Data Base
DF	Degrees of Freedom
DL	Dose Level
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DR3	Durable response rate at 3 months
DR6	Durable respone rate at 6 months
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

EFS	Event-free Survival
EOT	End of Treatment
EPO	Erythropoietin
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
IA	Investigator Assessment
ICH	International Conference on Harmonization
IEC/IRB	Independent Ethics Committee/Institutional Review Board
Ig	Immunoglobulin
IPI	International Prognostic Index
IR	Independent Review
IRC	Independent Review Committee
IWC	International Workshop Criteria
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Mieloma
MR	Major Response
MUGA	Multiple-gated Acquisition Scan
NA	Not Applicable
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NE	Not Evaluable
NOS	Not Otherwise Specified
ORR	Overall Response Rate
OS	Overall Survival
OS3	Overall Survival at 3 months

OS6	Overall Survival at 6 months
PD	Progressive Disease
PDy	Pharmacodynamics
PFS	Progression-free Survival
PFS3	Progression-free Survival at 3 months
PFS6	Progression-free Survival at 6 months
PK	Pharmacokinetics
PR	Partial Response
PS	Performance Status
RBC	Red Blood Cell
RD	Recommended Dose
RR	Response Rate
SAE(s)	Serious Adverse Event(s)
sCR	Stringent Complete Response
SD	Stable Disease
SOC	System Organ Class
SPD	Sum of the Product of the Diameters
StD	Standard Deviation
TTP	Time to Progression
TTO	Time to Onset
ULN	Upper Limit of Normal
US	United States
v	Version
VGPR	Very Good Partial Response
WBC	White Blood Cells
WHO	World Health Organization
wk	Week

1. STUDY RATIONALE

Multiple myeloma (MM) is a malignant plasma-cell disorder characterized by the production of a monoclonal protein from plasma cells in the bone marrow (BM). Information from the National Cancer Institute indicates that in the US, an estimated 22,350 new cases of MM will be diagnosed in 2013, and 10,710 people will die from the disease. The incidence of MM in Europe is 4.5-6.0/100,000 a year with a median age of diagnosis of between 63 and 70 years and a mortality rate of 4.1/100,000/year. In the Western hemisphere, about 1% of cancer-related deaths are due to myeloma. MM may be staged according to either the Durie-Salmon system (protocol appendix 4) based on the amount of abnormal monoclonal immunoglobulin in the blood or urine, blood calcium levels, the amount of bone damage shown by X-ray and blood hemoglobin levels, or the newer staging system, the International Staging System that relies on the levels of albumin and beta-2-microglobulin in the blood (protocol appendix 4). In both systems, all stages are further subclassified by creatinine level either less than 2.0 mg/dL or greater than or equal to 2.0 mg/dL. Impaired renal function worsens prognosis regardless of the stage.

The disease primarily affects individuals later in life with a median age of 63-70 years. From the time of diagnosis, survival without treatment is between 6 and 12 months and extends to 3 years with chemotherapy (CT). MM is treatable but rarely curable. Most patients receive multiple treatments over the course of their disease, and the precise sequence of therapy and used regimens can be quite variable. With standard dose CT, patients have a median survival of 24–30 months. Twenty five percent of patients survive 5 years or longer, and the 10-year survival rate is approximately 3%. Failure of standard therapy to cure these diseases has led to the study of higher doses of chemotherapeutic agents. These conditioning regimens may involve ablative/reduced or non-myeloablative intensity and the rescue of the immune system following CT may involve autologous or allogeneic stem-cell transplantation.

A full rationale for the study can be found in the appropriate sections of the study's protocol.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To determine the recommended dose (RD) of plitidepsin in combination with bortezomib and dexamethasone in patients with relapsed and/or refractory MM.

2.2. Secondary Objectives

- To determine the efficacy of plitidepsin in combination with bortezomib and dexamethasone.
- To evaluate the safety and tolerability of the combination in patients with relapsing and/or refractory MM.
- To study the pharmacokinetics (PK) and pharmacodynamics (PDy) of plitidepsin in combination with bortezomib and dexamethasone.

3. STUDY DESIGN

This is a multi-center, uncontrolled, single arm, phase I study, designed to establish the optimal dose of the combination plitidepsin, bortezomib and dexamethasone in patients with refractory and/or relapsed MM. Patients will be enrolled sequentially into three dose levels (DLs). The feasibility of administering plitidepsin with bortezomib in combination with dexamethasone and the RD of the combination will be determined. Patients will be evaluated at scheduled visits in three study periods: pre-treatment, treatment and follow-up.

Cohorts of three patients will be treated at each DL (up to three DLs) according to the next table:

DL	Number of Patients	Plitidepsin dose (mg/m^2)	Bortezomib dose (mg/m^2)	Dexamethasone dose (mg)
-1	0-6	3.0	1.0	40.0
1	3-6	4.0	1.0	40.0
2	3-6	4.0	1.3	40.0
3	3-6	5.0	1.3	40.0

DL; Dose level.

- The first cohort of three patients will start at DL1.
- If no DLTs are observed in any of the three patients at a given DL, three additional patients will be treated at the next DL.
- If a DLT is observed in one of three patients treated at a given DL, three additional patients will be entered at that same DL.
- If DLTs are observed in two of three patients, no additional patients will be treated at that DL and the immediately lower DL will be expanded to at least six patients.
- If two out of six patients have DLTs at DL1, the next patients enrolled will be treated at DL -1. If two out of six patients (≥33%) have DLTs at this DL, the study will be stopped and that DL will be considered the maximum tolerated dose (MTD).
- The RD is defined as the DL at which fewer than two out of six patients (33% of patients) experience DLTs during the first cycle.
- At the RD, at least six evaluable patients for the determination of DLTs will be treated.
- At DL1, one patient must have completed the first cycle before accrual of the second and third patients. The second and third patients may be treated simultaneously.
- Intermediate dose escalation or de-escalation is allowed.
- Intrapatient dose escalation is not allowed.

4. SAMPLE SIZE

A total of 20-30 patients are expected to participate. However, the number of patients may vary depending upon the tolerability of the combination and the number of DLs required to identify the RD.

5. STUDY ENDPOINTS

5.1. Primary Endpoint: Determination of the RD

- The RD will be the highest DL at which fewer than two out of six patients (33%) experience DLTs during the first cycle.

5.2. Secondary Endpoints

- Overall response rate (ORR), including sCR, CR, VGPR and PR.
- Minimal response (MR).
- Stable disease (SD).
- Clinical benefit rate, including ORR plus MR and SD.
- Duration of response (DOR).
- Time to progression (TTP).
- Progression-free survival (PFS).
- Event-free survival (EFS).

- Safety and tolerability.
- PK and PDy of plitidepsin in combination with bortezomib and dexamethasone.

6. PATIENT EVALUABILITY CRITERIA (POPULATIONS)

To be enrolled in this study, the patients must meet all inclusion criteria and no exclusion criteria.

6.1. Population Included

Defined as all patients who are enrolled in the study and have been recorded in the database, regardless of whether they have received study drugs.

6.2. Population Evaluable for RD

The main objective of the study (determination of the RD) will be assessed in this population.

Patients must be replaced if:

- They are withdrawn from the study due to not being evaluable for the primary endpoint, due to hypersensitivity reactions or reasons other than drug-related AEs meeting DLT criteria [e.g., consent withdrawal, not meeting the eligibility criteria, non-compliance with follow-up, early disease progression (PD), or unrelated AEs].

- They require radiation therapy or other anticancer procedure within four weeks after the first dose, unless they previously had another drug-related AE included in the definition of DLT.

- There is a protocol deviation/s precluding conclusions on the safety of the study therapy.

All replaced patients will be included in the general safety analysis and in the efficacy analysis (if appropriate).

6.3. Population Evaluable for Safety

Defined as all patients who have received at least one (complete or incomplete) dose of plitidepsin.

6.4. Population Evaluable for Efficacy

Although it is not the main objective of this study, antitumor activity will be measured clinically and/or radiologically according to IMWG. Patients will be evaluable for efficacy if they meet all inclusion criteria and no exclusion criteria and receive at least

one complete treatment cycle (two plitidepsin infusions, four bortezomib injections, four doses of dexamethasone) ***and have at least one disease assessment*** without protocol deviations with an effect on the risk/benefit ratio of the clinical trial, which may jeopardize the efficacy evaluation. Patients from this population who have inadequate post-baseline data to assess efficacy according to the response criteria (see section 6.1.1 of the protocol) will be considered treatment failures and will be included in the ORR and clinical benefit calculations.

7. GENERAL ANALYSIS METHODS

7.1. Statistical Software

Medidata Rave® electronic data capture (EDC) will be used for data entry and clinical data management. SAS® Software v9.2 or superior will be used for all statistical analyses.

7.2. Data Analysis Conventions

All data analysis conventions, derived data calculations and grouping needed at the time to perform the statistical analysis will be detailed in a separate document not included in this SAP called "data analysis conventions" (DAC).

8. STATISTICAL ANALYSIS

8.1. Patient Disposition and Protocol Deviations

A summary of patients and dose levels will be presented and organized by population type:

- Population included.
- Population evaluable for safety.
- Population evaluable for RD (primary endpoint population).
- Population evaluable for efficacy.

Patients who do not fit into any of these categories will be listed and the reasons for each of them will be detailed.

Accrual and study discontinuation details will be presented in a descriptive manner.

Reasons for treatment discontinuation will be summarized by counts and percentages and will be listed by number of cycles received. Treatment discontinuation for reasons other than disease progression will be detailed.

A protocol deviation is defined as any departure from what is described in a clinical trial protocol that has been approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB) and a Competent Authority. Therefore, it applies to deviations from patient inclusion criteria and clinical procedures (e.g., assessments to be conducted or parameters to be determined), and also to any other procedure described in the protocol and concerning Good Clinical Practice (GCP) guidelines or ethical issues (e.g., issues related to obtaining the patients' Informed Consent, data reporting, Investigator's responsibilities etc.).

Protocol deviations will be classified mainly based on the following group categories [as defined by International Conference on Harmonization (ICH) E-3]. However, other relevant groups could be added.

- Inclusion/exclusion criteria not met.

- Withdrawal criteria met, but treatment continued.

- Incorrect treatment, dose or schedule received.

- Excluded concomitant medication received.

- Failure to comply study procedures.

- Any other relevant subgroup defined at revision.

8.2. Baseline Characteristics

8.2.1 Demographics

Demographics and baseline characteristics will be summarized for all patients included. All patients' characteristics will be presented by DL or by most adequate dose grouping according to the number of finally treated patients.

Continuous variables will be summarized and presented by means of summary statistics, i.e., mean, median, range and standard deviation if appropriate.

Categorical variables will be summarized in frequency tables, where percentages will be rounded to one decimal and may therefore not always add up to exactly 100%.

When multiple baseline values are available (e.g. laboratory measurements, vital signs), the last value prior to or on the first day of treatment will be selected as baseline value.

Baseline Eastern Cooperative Oncology Group (ECOG) scores will be summarized by frequency counts.

MM history, histology, time from diagnosis, number of baseline lesions and different site involvement will be summarized by means of frequency tables or summary statistics. Time from initial diagnosis to the start of study treatment and time from the

latest disease progression to the start of study treatment will be shown in months and summarized descriptively. Incomplete dates should be recorded following imputation rules described in Section 9.2.

Relevant medical history (other than MM) will be displayed in frequency tables by dose level (or the most adequate dose grouping) and by patient.

Previous surgery, radiotherapy or other anticancer therapy (number of lines and number of agents) will be summarized in a frequency table. To ensure the accurate analysis of the number of chemotherapy agents and lines, these will be revised and if necessary recoded by PharmaMar's physicians.

Signs and symptoms, hematology and serum biochemistry abnormalities at baseline will be displayed in frequency tables according to NCI-CTCAE v4 toxicity grades. Grade ≥2 signs and symptoms and laboratory abnormalities at baseline will be listed by dose level (or the most adequate dose grouping).

8.3. Statistical Analysis for Safety

Safety variables will be analyzed in a descriptive way. Data retrieved from scheduled and unscheduled visits will be tabulated by dose level (or by most adequate dose grouping).

All patients who receive at least part of a plitidepsin infusion will be evaluable for safety and will be included in the general safety displays.

Patients evaluable for RD will be used for the primary analysis.

For the evaluation of the main endpoint, the total number of patients included, the number of patients evaluable for determination of DLTs and the number of patients with any DLT (and their categorization) will be summarized by dose level (or the most adequate dose grouping). Toxicities meeting the DLT criteria in Cycle 1 and toxicities in subsequent cycles, if any, will be listed separately, and the description of laboratory abnormalities (hematology / biochemistry) will be supported by graphs depicting the evolution in time of laboratory values (including nadir calculation and median time to recovery from baseline values).

8.3.1 Treatment Administration and Exposure

Patient exposure to plitidepsin, bortezomib and dexamethasone will be summarized by dose level for the safety population.

Total cumulative Plitidepsin dose, expressed in mg/m^2, defined as the sum of all the Plitidepsin doses from the first to the last dose received.

Total cumulative Bortezomib dose, expressed in mg/m^2, defined as the sum of all the Bortezomib doses from the first to the last dose received.

Total cumulative Dexamethasone dose, expressed in mg, defined as the sum of all the Dexamethasone doses from the first to the last dose received.

Intended Plitidepsin dose intensity, is the planned dose for a particular cycle divided by the planned duration of a cycle in weeks. Expressed in mg/m^2/wk.

Intended Bortezomib dose intensity, is the planned dose for a particular cycle divided by the planned duration of a cycle in weeks. Expressed in mg/m^2/wk.

Intended Dexamethasone dose intensity, is the planned dose for a particular cycle divided by the planned duration of a cycle in weeks. Expressed in mg/week (wk).

Absolute Plitidepsin dose intensity, is the total cumulative dose divided by the treatment duration, expressed in mg/m^2/wk. As a convention, the duration of the last cycle is considered to be 28 days (planned cycle duration).

Absolute Bortezomib dose intensity, is the total cumulative dose divided by the treatment duration, expressed in mg/m^2/wk. As a convention, the duration of the last cycle is considered to be 28 days (planned cycle duration).

Absolute Dexamethasone dose intensity, is the total cumulative dose divided by the treatment duration, expressed in mg/wk. As a convention, the duration of the last cycle is considered to be 28 days (planned cycle duration).

Relative Plitidepsin / Bortezomib / Dexamethasone dose intensity (%), is the ratio resulting from the absolute dose intensity divided by the intended dose intensity.

Time on treatment: is the interval, expressed in weeks, between the first infusion date and the last infusion date plus 30 days or the start of new treatment or the date of death (whichever occurs first).

Depending on the number of patients cases mean, median, minimum and maximum values or standard deviation for the parameters defined above will be tabulated by dose level (or the most adequate dose grouping).

8.3.2 Cycle Delays and Omissions

Whenever a dose delay for Day 1 has been ticked on the electronic case report form (eCRF) field "Infusion delayed: No/Yes" the length of the delay will be calculated as follows:

Cycle delay (days) = [current cycle's start date] – [previous cycle's start date] - 28 days (planned cycle duration)

A cycle delay is defined as a delay in the administration of the first infusion in one cycle (i.e. Day 1 infusion).

Cycle 1 will be excluded from all calculations of cycle delays. Therefore, the denominator used in all cycle delay calculations will exclude Cycle 1 and be equal to the number of cycles susceptible to be delayed.

Dose delays distribution with respect to any given cycle will be studied by means of counts and percentages. The reasons for cycle delays will be detailed, specifying how many were due to treatment-related toxicity. Other reasons (e.g. administrative reasons) will be analyzed separately and additional tables will be prepared. Dose delays attributed to study treatment will be detailed, and hematological and/or non-hematological reasons will be outlined.

Dose skipping or dose omission is defined as any infusion not administered, including the second infusion of the first cycle. The distribution of skipped doses with respect to any given cycle will be studied by means of counts and percentages (the denominator used for calculations will be equal to the number of patients/cycles susceptible to have an omission). A detailed listing of patients with skipped doses and reasons as well as reasons for dose omission will be shown.

8.3.3 Dose Reductions

All Plitidepsin/Bortezomib/Dexamethasone dose reductions will be considered and described (per cycle and patient), specifying the magnitude and the reason/s for treatment-related dose reductions (hematological toxicity, non-hematological toxicity or both), or any other causes unrelated to treatment. The denominator used in all dose reduced calculations will be equal to the number of cycles susceptible to be reduced, it means, the Cycle 1 will be taken into account for dose reduction calculations if more infusions than the first infusion of Cycle 1 were taken.

The distribution of plitidepsin/bortezomib/dexamethasone dose reductions in any given cycle will be studied by means of counts and percentages.

8.3.4 Dose Interruptions

All dose interruptions will be listed by patient and compound (Plitidepsin/Bortezomib/Dexamethasone).

8.3.5 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Toxicity evaluation will be done in accordance with NCI-CTCAE v.4. Otherwise, severity will be noted. As a convention, the term "Grade" will always be used, according to the worst NCI-CTCAE grade or, for toxicities which do not form the subject of NCI-CTCAE classification, according to the worst severity.

Descriptive statistics will be used for the evaluation of safety. AEs and laboratory abnormalities will be displayed in frequency tables using counts and percentages and will be graded to the most severe grade per patient and cycle. A separate analysis will be done for Cycle 1. The worst grade reached by each patient during Cycle 1 will also be shown.

Shifts in severity grades from baseline to worst occurrence during treatment, deaths, serious adverse events (SAEs) and events resulting in study discontinuation will be tabulated.

In order to clearly define the safety profile of Plitidepsin, additional safety analyses, as well as additional classifications other than System Organ Class (SOC)/Preferred Term (PT) may be added, if necessary.

8.3.6 Serious Adverse Events (SAEs)

Database listings of deaths and SAEs will be provided and will include at least onset and resolution dates (if applicable), severity, relationship to study drug, most important significant consequence and main action taken.

If enough number of SAEs are reported, they will be displayed in frequency tables using counts and percentages and will be graded to the most severe grade per patient and cycle.

8.3.7 Laboratory Evaluations

8.3.7.1 Hematology

Hematological toxicities will be classified according to NCI-CTCAE v.4, and will be presented by cycle and dose level (or the most adequate dose grouping). A separate analysis will be done for Cycle 1. The worst grade reached by each patient during Cycle 1 will also be shown.

If serious hematological toxicities occur, a special follow-up will be done to determine the pattern of thrombocytopenia and neutropenia within and between the different cycles. This follow-up will include the calculation of mean, standard deviation, median and the range of nadir values and of the time to recovery to baseline values.

Descriptive tables, and supporting, graphic representations of nadir values for neutrophil and platelet counts (by cycle dose level or the most adequate dose grouping) will be used. Also inter-cycle time courses for neutropenia, thrombocytopenia or any other significant parameter will be displayed in graphs. If necessary, graphs comparing first and second cycle time courses for these parameters will be created.

Shifts in severity grades from baseline to worst occurrence during treatment will be tabulated.

8.3.7.2 Serum Biochemistry and Coagulation Tests

Non-hematological laboratory abnormalities [e.g. transaminases, creatinine, creatine phosphokinase (CPK), bilirubin, AP, etc.] will be classified according to NCI-CTCAE v.4 and will also be shown by patient and cycle. A separate analysis will be done for Cycle 1. The worst grade reached by each patient during Cycle 1 will also be shown.

If serious non-hematological toxicities occur, a special follow-up will be done that will include the calculation of mean, standard deviation, median and range of peak values, as well as the time to recovery to baseline values.

Descriptive tables will be used to determine toxicity patterns within and between cycles. These tables can be complemented with boxplots that help display peak values of transaminases, creatinine, CPK, bilirubin, AP, etc. by cycle, dose level or the most adequate dose grouping. Also, inter-cycle time course graphs for any significant parameter, as well as graphs comparing first and second cycle time courses will be created.

Shifts in severity grades from baseline to worst occurrence during treatment will be tabulated.

8.3.7.3 Physical Examination

The evaluation of physical examination (i.e., normal/abnormal) will be summarized with frequency counts. All data will be listed by dose level.

8.3.7.4 Electrocardiogram (ECG) / Left Ventricular Ejection Fraction (LVEF)

Baseline ECG evaluation (normal/abnormal) will be summarized with frequency counts.

Continuous variables (PR Interval, QT Interval, QRS Complex, Ventricular Rate, LVEF and LVEF Normal Range) will be summarized and summary statistics will be provided (i.e., median and range). Baseline values and their evolution during treatment will be tabulated with summary statistics.

Corrected QT interval (QTc) will be calculated in the database by using Bazett's formula.

8.3.4.5 Vital Signs

Performance status (PS) and weight gain / loss during the study will be summarized by frequency tabulation.

8.3.4.5 Concomitant Medication

Concomitant therapies will be coded using the World Health Organization Anatomical Therapeutic Chemical Classification System (WHO-ATC) dictionary and categorized according to ATC class (levels 1, 2 and 4). The number of patients receiving each type of therapy will be tabulated in two separated frequency tables: one for therapies that

started pre-study, and another one for those administrated during the study. The accompanying listing will include all concomitant therapies.

Additional listings for patients taking prohibited medications / therapies according to protocol will be provided.

8.4 Statistical Analysis for Efficacy

8.4.1 Exploratory Analysis of Antitumor Activity

The efficacy population is defined as all eligible patients who have received at least one treatment cycle and without protocol deviations with an effect on the risk/benefit ratio of the clinical trial, which may jeopardize the efficacy evaluation. Patients from this population who have inadequate post-baseline data to assess efficacy according to the response criteria in Section ***6.1.1.*** of the protocol will be considered treatment failures and will be included in the ORR and clinical benefit calculations.

ORR and clinical benefit rate will be calculated and binomial exact confidence intervals at 95% will be presented.

Follow-up time will be calculated from the date of the first infusion to the date of the last documented examination. The DOR will be analyzed for all patients in whom a response has been observed and will be calculated from the date of the first documentation of response to the date of PD or further therapy or death.

TTP will be calculated from the date of the first infusion to the date of documented PD or death due to PD. PFS will be calculated from the date of the first infusion to the date of documented PD or death (regardless of the reason). Likewise, EFS will be calculated from the date of first infusion to the date of documented PD or death but may include additional events besides death and PD that are considered of importance. If any patient is lost to follow-up before PD or receives another antitumor therapy, the TTP, PFS or EFS will be censored on the date of the last tumor assessment. If there are no tumor assessments, these parameters will be censored on the date of the first drug administration.

Median time to onset and duration of response, time to PD, PFS, EFS and estimated rate of patients free of progression will be calculated by Kaplan-Meier estimates with 95% confidence intervals.

8.4.2 Level of Significance

Confidence intervals will be constructed using the 95% level. No formal statistical tests are defined, but if needed, all will be done at a significance level of 5% (two-sided) and will be considered exploratory.

9 OTHER STATISTICAL ANALYSIS

9.1 Subgroup Analysis

Exploratory subgroup analysis will be done to compare refractary myeloma patients *vs.* relapsed myeloma patients. It is also planned to gather information about the type of myeloma, since it can be secretory or non-secretory. According to information given by the physician, it is expected to find 97–98% of secretory myelomas and 2–3% of non-secretory myelomas, evaluating both of them with different methods, according to IMWG criteria.

Non-scheduled analyses could be performed, if considered necessary to enhance the patient's safety/efficacy.

9.2 Missing Values Management

Missing laboratory values will be subtracted from the denominator of the tables.

Imputation of Incomplete Dates

Dates before registration

If the day of a month is unknown, the imputed day will be the 15th of that month. If the month is also unknown, the imputed date will be the 1st of July. This assumption will only be valid if the imputed date is earlier than the date of the patient's informed consent; otherwise, the imputed date will be the first day of the month in which the informed consent was signed (i.e., 01/ date of signing of the informed consent/year).

Dates after the end of treatment

To ensure the most conservative approach for the efficacy time-to-event variables (e.g., PFS), which can be affected by missing values, the following rules will be followed: if the day of a month is unknown, then the imputed day will be the 1st; if the month is also unknown, then the imputed date will be the 1st of July. This assumption will be valid if the imputed date occurs later than the last drug administration date; otherwise, the imputed date will be the date of the last drug administration plus one.

9.3 Decimals

By default, all numeric results will be rounded to one decimal point, except when variables are integer; in which case, they will be reported without decimals; e.g. age in years, number of sites, tumor size in mm for target lesions etc.

9.4 Output Formats

Tables, listings and graphs could be performed by MM type. Dose levels or any variable susceptible to be grouped (e.g. toxicity grades) may be joined to add clarity to the reported tables. Table formats could also be modified to clarify the reported information (e.g. if dose level sample sizes ≤3 then the only percentage shown will be the total

column percentage, for the others, only the number of patients will be shown), if appropriate. Table categories will usually be ordered by descending frequency. If appropriate, continuous variables could be complemented with mean, standard deviation or 95% CIs. Likewise, the range of continuous variables with only one observation might be deleted to avoid duplicated information. The structure of the tables and the graphs is given as an example. Changes may be done in order to improve interpretation of the results.

APPENDIX I

10 Appendix I. Patients Disposition

The general characteristics analysis will be presented on the included population.

10.1 General Characteristics

10.1.1 Patient Disposition

Main characteristics concerning inclusion in the study, withdrawal from the study and protocol deviations will be displayed in this section.

Table 10.1.1.1 Included and evaluable patients by dose level.

Included and evaluable patients	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Included				
Evaluable for RD				
Evaluable for Safety				
Evaluable for Efficacy				

Table 10.1.1.2 Patients not Evaluable for RD.

Patient No	Criteria number/s and description

Table 10.1.1.3 Patients not evaluable for Safety.

Patient No	Criteria number/s and description

Table 10.1.1.4 Patients not evaluable for Efficacy.

Patient No	Criteria number/s and description

Table 10.1.1.5 Patient Accrual by Institution and Dose Level

	Dose level*

	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Institution Institution 1				
Institution 2				
….				
Total				

Notes: Percentage is based on number of patients by dose level.
(*) The actual dose level in mg/m^2 will be shown in all headings for all tables in sections 10, 11 and 12.

Table 10.1.1.6 Patient Accrual by Country and Dose Level

	Dose level*			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Country Country 1				
Country 2				
….				
Total				

Notes: Percentage is based on number of patients by Dose Level
(*) The actual dose level in mg/m^2 will be shown in all headings for all tables in sections 10, 11 and 12.

Table 10.1.1.7 Study dates

Dates information
Date of first consent
Date of first dose
Date of last consent
Date of first dose of last patient
Date of last dose
Date of last follow up*

(*) Last follow up, examination or procedure before study closure.

Table 10.1.1.8 Time on Treatment (Weeks) by Dose Level

Median and Range of Time on treatment (days)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Median				
Min				
Max				

10.1.2 Treatment Discontinuations

Table 10.1.2.1 Treatment Discontinuation by Dose Level

Treatment discontinuation	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Progressive disease				
Treatment related AE				
Non-treatment related AE				
Patient refusal				
Death				
Investigator's decision				
Other				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 10.1.2.2 Treatment Discontinuation Details

Patient No	Last cycle infused	Treatment discontinuation reason	Details

Table 10.1.2.3 Reasons for Treatment Discontinuation by Cycle and Dose Level (all Treated Patients)

Treatment discontinuation		Dose level			
		I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
		N(%)	N(%)	N(%)	N(%)
Progressive disease	1 cycle				
	2-3 cycles				
	>=4 cycles				
Patient refusal to treatment	1 cycle				
	2-3 cycles				
	>=4 cycles				
Investigator's decision	1 cycle				
	2-3 cycles				
	>=4 cycles				
Toxicity	1 cycle				
	2-3 cycles				
	>=4 cycles				
Death	1 cycle				
	2-3 cycles				
	>=4 cycles				
Other	1 cycle				
	2-3 cycles				
	>=4 cycles				
Total					

Notes: Percentage is based on number of patients by Dose Level

Table 10.1.2.4 Treatment Discontinuation Due to Adverse Events

Dose level	Patient id.	SOC	MedDra PT	Relationship	….

Table 10.1.2.5 Reasons for Treatment Discontinuation Other Than Progressive Disease

Dose Level	Patient No	Last cycle infused	End of study reason	Specify

Table 10.1.2.6 Study Discontinuation. Specify

Dose Level	Patient No	Study discontinuation date	Study discontinuation reason	Off-Study reason

Table 10.1.2.7 Reasons for Study Discontinuation by Dose Level

Study discontinuation	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
End of Study				
Patient refusal				
Investigator's decision				
Lost to follow up				
Death				
Other				
Total				

10.1.3Protocol Deviations

Table 10.1.3.1 Protocol Deviations. Ineligible Patients as Per Protocol by Dose Level

Ineligible patients as per protocol	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Protocol deviation				

Ineligible patients as per protocol	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Without deviation				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 10.1.3.2 Protocol Deviations. Patients Not Withdrawn as Per Protocol by Dose Level

Patients not withdrawn	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Protocol deviation				
Without deviation				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 10.1.3.3 Protocol Deviations. Incorrect Dose or Schedule by Dose Level*

Incorrect dose or schedule	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Protocol deviation				
Without deviation				
Total				

Notes: Percentage is based on number of patients by Dose Level
* Including patients not meeting criteria for re-treatment.

Table 10.1.3.4 Protocol Deviations. Patients Receiving Prohibited Concomitant Medication by Dose Level

Excluded Concomitant Medication	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Protocol deviation				
Without deviation				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 10.1.3.5 Supportive Listing Protocol Deviations.

Dose level	Patient No	Protocol deviation type	Specify

Dose level	Patient No	Protocol deviation type	Specify

10.2 Patient Characteristics

10.2.1 Patient Characteristics at Baseline

Table 10.2.1.1 Age at Entry by Dose Level

Age at entry	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
18 - XX years				
XX-YY years				
…				
>= ZZ years				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.1.2 Age Mean, Median, Std and Range by Dose Level

Age median and range	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Mean				
Median				
Std				
Min				
Max				

Table 10.2.1.3 Race by Dose Level

Race	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Caucasian				
Black				
Asian				
…				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.1.4 Gender by Dose Level

Gender	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Male				

Gender	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Female				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.1.5 ~~Relapse~~Relapsed / Refractory Disease by Dose Level

Type	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Primary refractory myeloma				
Relapsed and refractory myeloma				
Relapsed myeloma				
Total				

Notes: Percentage is based on number of patients by Dose Level

10.2.2Multiple Myeloma History

Table 10.2.2.1 Time from Diagnosis to First Infusion (months) by Dose Level

Time from Diagnosis to First Infusion	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
N				
Mean				
Median				
Std				
Min				
Max				

Table 10.2.2.2 Time from last PD (months) by Dose Level

Time from last PD	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
N				
Mean				
Median				
Std				
Min				
Max				

Table 10.2.2.3 Multiple Myeloma Type by Dose Level

Multiple Myeloma Type	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
IgG				
IgA				
Light Chain Disease				
IgD				
IgE				
IgM				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.2.4 Durie-Salmon stage at First Diagnosis by Dose Level

Durie-Salmon Stage	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
I				
II				
III				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.2. 5 Durie-Salmon Sub-classification at First Diagnosis by Dose Level

Durie-Salmon Sub-classification	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
A				
B				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.2.6 ISS stage at First Diagnosis by Dose Level

ISS Stage	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
I				
II				
III				
Not Done				
Total				

Notes: Percentage is based on number of patients by Dose Level

10.2.3Prior Anticancer Therapy: Palliative Radiotherapy

Table 10.2.3.1 Previous Treatment Summary by Dose Level

Previous Palliative Radiotherapy	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Yes				
No				
Total				

Notes: Percentage is based on number of patients by Dose Level

10.2.4Prior Anticancer Medical Therapy

Table 10.2.4.1 Autologous and/or allogeneic hematopoietic stem cell transplantation (HSCT) by Dose Level

HSCT	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Autologous HSCT				
Allogenic HSCT				
Both				
Total				

Table 10.2.4.2 Previous Anticancer Therapy by Dose Level

Therapy Type	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Induction				
Consolidation				
Maintenance Therapy				
Rescue Therapy				
Total				

Notes: Production of this table will need a clinical review to classify all therapies in the aforementioned categories (not recorded in the CRF).

Table 10.2.4.3 Agents of Previous Chemotherapy (ATC level 1 & 4) by Dose Level

Medication	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
ATC level 1				

Medication	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
ATC level 4				
…				
…				
…				
…				
ATC level 4				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.4.4 No of Lines of Prior Chemotherapy by Dose Level

No of lines	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
01 lines				
02 lines				
…				
N lines				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.4.5 Summary Statistics. No of Lines of Prior Chemotherapy by Dose Level

Median and range for No of lines	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Median				
Mean				
Std				
Min				
Max				

Table 10.2.4.6 No of Agents of Prior Chemotherapy by Dose Level

No of agents*	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
01 agent				
02 agents				
…				
…				
…				
…				
N agents				
Total				

Notes: Percentage is based on number of patients by Dose Level. An agent used more than one will count 1once will count as 1.

Table 10.2.4.7 Summary Statistics. No of Agents of Prior Chemotherapy by Dose Level

Median and range for No of agents	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Mean				
Median				
Std				
Min				
Max				

Table 10.2.4.8 Supportive Listing: Previous Anticancer Therapy

Patient No	Not done	Type	Literal	Start date	End date	Best response	PD applicable	PD date

Notes: Production of this table will need a clinical review to classify all therapies in the aforementioned categories (not recorded in the CRF).

Table 10.2.4.8 Best Response to last Prior Anticancer Medical Therapy

Best Response	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Response Criteria for Multiple Myeloma				
sCR				
CR				
VGPR				
PR				
MR				
SD				
PD				
NE/NA				
Total				

10.2.5Physical Examination, Vital Signs, Electrocardiogram and Other Tests

Table 10.2.5.1 Physical Examination at baseline by Dose Level

Physical Examination	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Normal				
Abnormal				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.5.2 Weight at baseline by Dose Level

Weight (Kg)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Median				
Mean				
Std				
Min				
Max				

Table 10.2.5.3 Height at baseline by Dose Level

Height (cm)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Median				
Mean				
Std				
Min				
Max				

Table 10.2.5.4 Body Surface Area (BSA) at baseline by Dose Level

BSA (m^2)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Median				
Mean				
Std				
Min				
Max				

Table 10.2.5.5 Supportive Listing: Physical Examination Abnormal

Patient No	Date of physical exam	Weight	Height	Body surface area

Table 10.2.5.6 ECOG PS at baseline by Dose Level

ECOG PS	Dose level

	I (N=XX) N(%)	II (N=XX) N(%)	III (N=XX) N(%)	Total (N=XX) N(%)
0				
1				
…				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.5.7 Supportive Listing: Patients with PS ≥ 1 at baseline

Dose level	Patient No	Performance status

Table 10.2.5.8 Electrocardiogram Measures at baseline.

Dose level	Patient	Cycle	PR interval	RR interval	…	Max height of QRS complex

Table 10.2.5.9 Electrocardiogram Results at baseline by Dose Level (After Plitidepsin Administration).

Electrocardiogram Results	Dose level						
	I (N=XX) N(%)	II (N=XX) N(%)	III (N=XX) N(%)	… (N=XX) N(%)	… (N=XX) N(%)	N (N=XX) N(%)	Total (N=XX) N(%)
Normal							
Significant Abnormalities							
Non-significant Abnormalities							
Total							

Table 10.2.5.10 Supportive Listing: Electrocardiogram Abnormalities at baseline

Dose level	Patient No	Abnormality Specification

Table 10.2.5.11 Left Ventricular Ejection Fraction (LVEF) at baseline

LVEF	Dose level			
	I (N=XX) N(%)	II (N=XX) N(%)	III (N=XX) N(%)	Total (N=XX) N(%)
Normal				
Significant Abnormalities				
Non-significant Abnormalities				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.5.12 Mean, Median, Std and Range values of Left Ventricular Ejection Fraction (LVEF) at baseline (MUGA)

MUGA	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Mean				
Median				
Std				
Minimum				
Maximum				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.5.13 Mean, Median, Std and Range values of Left Ventricular Ejection Fraction (LVEF) at baseline (ECHO)

ECHO	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Mean				
Median				
Std				
Minimum				
Maximum				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.5.14 Baseline Characteristics: Pregnancy Test by Dose Level

Pregnancy Test	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Positive				
Negative				
NA*				
Total				

Notes: Percentage is based on number of patients by Dose Level
(*) Specify reasons

Table 10.2.5.15 Supportive Listing: Pregnancy Test by Dose Level

Dose level	Patient No	Reason

10.2.6Hematological evaluation at baseline

Table 10.2.6.1 Hematology Abnormalities at Baseline by Dose Level

Abnormality	Dose Level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Anemia				
Grade 1 - 4, N(%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
Leukopenia				
Grade 1 - 4, N(%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
…				
Grade 1 - 4, N(%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
XXXXXXX				
Grade 1 - 4, N(%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.6.2 Summary for Hematology Parameters at Baseline by Dose Level.

Mean, Median, Std and Range by abnormality	Dose Level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Hemoglobin				
N				
Mean				
Median				
Std				
Min				
Max				
WBC				
N				
Mean				
Median				
Std				
Min				
Max				

Mean, Median, Std and Range by abnormality	Dose Level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Lymphocytes				
N				
Mean				
Median				
Std				
Min				
Max				
…				
N				
Mean				
Median				
Std				
Min				
Max				
XXXXXXX				
N				
Mean				
Median				
Std				
Min				
Max				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.6.3 Supportive Listing: Patients with grade >=2 Hematology Abnormalities at Baseline

Dose level (mg /m²)	Patient	Lab. test	Examination date	N	Std. value	xLLN	Grade CTC v4.0

10.2.7Biochemical evaluation at baseline

Table 10.2.7.1 Biochemical Abnormalities at Baseline by Dose Level

Abnormality	Dose Level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
ALT increase				
Grade 1 - 4, N(%)				

Abnormality	Dose Level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Grade 1				
Grade 2				
Grade 3				
Grade 4				
AST increase				
Grade 1 - 4, N(%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
…				
Grade 1 - 4, N(%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
XXXXXXX				
Grade 1 - 4, N(%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.7.2 Biochemical Abnormalities at Baseline by Dose Level for patients with creatinine <2mg/dl

Abnormality	Dose Level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
ALT increase				
Grade 1 - 4, N(%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
AST increase				
Grade 1 - 4, N(%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
…				
Grade 1 - 4, N(%)				
Grade 1				
Grade 2				

Abnormality	Dose Level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Grade 3				
Grade 4				
XXXXXXX				
Grade 1 - 4, N(%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.7.3 Biochemical Abnormalities at Baseline by Dose Level for patients with creatinine ≥2mg/dl

Abnormality	Dose Level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
ALT increase				
Grade 1 - 4, N(%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
AST increase				
Grade 1 - 4, N(%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
…				
Grade 1 - 4, N(%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
XXXXXXX				
Grade 1 - 4, N(%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				

Notes: Percentage is based on number of patients by Dose Level

Table 10.2.7.4 Summary for Biochemical Parameters at Baseline by Dose Level

Median and Range	Dose Level

by abnormality	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
ALT				
N				
Mean				
Median				
Std				
Min				
Max				
AST				
N				
Mean				
Median				
Std				
Min				
Max				
…				
N				
Mean				
Median				
Std				
Min				
Max				
XXXXXXX				
N				
Mean				
Median				
Std				
Min				
Max				

Table 10.2.7.5 Supportive Listing: Patients with grade >=2 Biochemistry Abnormalities at Baseline

Dose level (mg/m²)	Patient	Lab. test	Examination date	N	Std. value	xULN	Grade CTC v4.0

10.2.8Signs and Symptoms at Baseline

11 Table 10.2.8.1 Incidence of Signs and Symptoms by Dose Level Worst Per Patient

MedDRA System Organ Class Preferred Term	I (N=XX) Grade					II (N=XX) Grade					…	Total (N=XX) Grade				
	1-4 N(%)	1 N(%)	2 N(%)	3 N(%)	4 N(%)	1-4 N(%)	1 N(%)	2 N(%)	3 N(%)	4 N(%)		1-4 N(%)	1 N(%)	2 N(%)	3 N(%)	4 N(%)
											…					

12 Notes: Percentage is based on number of patients by Dose Level

Table 10.2.8.2 Listing of Signs and Symptoms

Dose Level	Patient No	Not done	N	Literal	MedDRA Preferred Term	CTC v4.0 grade	Start date	Disease Related

Table 10.2.8.3 Summary of Signs and Symptoms by Dose Level

	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
No. signs				
1				
2				
…				
…				
…				
N				
Total				
No. signs				
N				
Mean				
Median				
Std				
Range				

Notes: Percentage is based on number of patients by Dose Level

10.3 Concomitant Medication Starting Pre-Study

Table 10.3.1 Concomitant Medication Starting Pre-Study (ATC Level 1, 2 and 4) by Dose Level

Medication Term (ATC level 1)	Medication Term (ATC level 2)	Medication Term (ATC level 4)	Dose level			
			I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
			N(%)	N(%)	N(%)	N(%)

Notes: Percentage is based on number of patients by Dose Level

Table 10.3.2 Concomitant Medication Starting Pre-Study (Patients with transfusions and ATC Level 1, 2 and 4) by Dose Level

Medication Term (ATC level 1)	Medication Term (ATC level 2)	Medication Term (ATC level 4)	Dose level			
			I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
			N(%)	N(%)	N(%)	N(%)
Platelet transfusion						
RBC transfusion						
…						

Notes: Percentage is based on number of patients by Dose Level

Table 10.3.3 Supportive Listing: Patients with transfusions (Pre-Study)

Patient No	Not done	Type	Literal	Route	Specify of route	Dose	Unit	Start date (text)	Start date ongoing	End date (text)	End date ongoing	Reason

11 Appendix II. Safety Evaluation

This analysis will be presented on the evaluable for safety population.

11.1 Extent of Exposure

11.1.1 Cumulative Dose, Dose Intensity and Relative Dose Intensity

Table 11.1.1.1 No of cycles administered

		Patients
Dose level	Max cycle infused	No of patients
I	Cycle 1	
	Cycle 2	
II	Cycle 1	
	Cycle 2	
III	Cycle 1	
	Cycle 2	
…	Cycle 1	
	Cycle 2	
N	Cycle 1	
	Cycle 2	
Total	Cycle 1	
	Cycle 2	
	Cycle 3	
	…	
	Cycle N	

Table 11.1.1.2 Supportive Listing: No of Patients by Dose Level

Dose level	Patient Id	Evaluable for safety (Y/N)	Evaluable for DLT (Y/N)
I			
II			
III			
…			
…			
N			

Table 11.1.1.3 Number of Cycles Administered by Dose Level

No cycles administered per patient	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N (%)	N (%)	N (%)	N (%)
1 Cycle				
2 Cycles				
3 Cycles				
…				
…				
N Cycles				

Notes: Percentage is based on number of patients by Dose Level

Table 11.1.1.4 Mean, Median, Std and Range of Cycles Administered by Dose Level

Mean, Median , Std and range of cycles administered	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Mean				
Median				
Std				
Min				
Max				

Table 11.1.1.5 Plitidepsin Cumulative Dose by Dose Level

Plitidepsin Cumulative dose (mg/m^2)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Mean				
Median				
Std				
Min				
Max				

Table 11.1.1.6 Bortezomib Cumulative Dose by Dose Level

Bortezomib Cumulative dose (mg/m^2)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Mean				
Median				
Std				
Min				
Max				

Table 11.1.1.7 Dexamethasone Cumulative Dose by Dose Level

Dexamethasone Cumulative dose (mg)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Mean				
Median				
Std				
Min				
Max				

Table 11.1.1.8 Plitidepsin Intended Dose by Dose Level

Plitidepsin Intended dose (mg/m²/week)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Mean				
Median				
Std				
Min				
Max				

Table 11.1.1.9 Bortezomib Intended Dose by Dose Level

Bortezomib Intended dose (mg/m²/week)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Mean				
Median				
Std				
Min				
Max				

Table 11.1.1.10 Dexamethasone Intended Dose by Dose Level

Dexamethasone Intended dose (mg/week)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Mean				
Median				
Std				
Min				
Max				

Table 11.1.1.11 Plitidepsin Relative Dose Intensity by Dose Level

Plitidepsin Absolute Dose Intensity (mg/m²/week)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Mean				
Median				
Std				
Min				

Plitidepsin Absolute Dose Intensity (mg/m²/week)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Max				

Table 11.1.1.12 Bortezomib Relative Dose Intensity by Dose Level

Bortezomib Absolute Dose Intensity (mg/m²/week)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Mean				
Median				
Std				
Min				
Max				

Table 11.1.1.13 Dexamethasone Relative Dose Intensity Dose Level

Dexamethasone Absolute Dose Intensity (mg/week)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Mean				
Median				
Std				
Min				
Max				

Table 11.1.1.14 Supportive Listing: Drug Administration: Patients with Less Than 60% of Dose Intensity

Dose level	Patient No	Agent	Cycle	Date	Intended dose (mg /m²)	Total dose (mg /m²)	Delay	Delay specify	Dose modification	Dose modification specify

11.1.2Cycle Delays

Table 11.1.2.1 No of Patients with Dosing Delayed by Dose Level

No. of patients	Dose level

with dosing delayed	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
No				
Yes				
Any DR*				
All NDR**				
Total				

* Drug related ** Non drug related.

Table 11.1.2.2 No of Cycles with Dosing Delayed by Dose Level

No of cycles with dosing delayed	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
No				
Yes				
Drug Related				
Hematological				
Non Hematological				
Both				
Non Drug Related				
Total				

Table 11.1.2.3 No of Cycles Delayed Per Patient by Dose Level

No patients with :	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
No cycle delayed				
01 cycle delayed				
02 cycles delayed				
…				
…				
Total				
Mean				
Median				
Std				
Min				
Max				

Table 11.1.2.4 Number of Cycles with Drug Related Delay per patient by Dose Level

No patients with :	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
No cycle delayed				

No patients with :	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
01 cycle delayed				
02 cycles delayed				
…				
…				
Total				
Mean				
Median				
Std				
Min				
Max				

Table 11.1.2.5 Length of Delay by Dose Level

Length of delay	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Mean				
Median				
Std				
Min				
Max				

Table 11.1.2.6 Length of Delay for Drug Related Events by Dose Level

Length of delay	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Hematological				
N				
Median				
Min				
Max				
Non Hematological				
N				
Median				
Min				
Max				
Both				
N				
Median				
Min				
Max				
Total				
N				
Median				
Min				

Length of delay	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Max				

Table 11.1.2.7 Supportive Listing: Drug Administration: Dose Delays

Dose level	Patient No	Agent	Cycle	Date	Intended dose (mg /m²)	Total dose (mg /m²)	Length of Delay	Delay Reason	Delay specify

11.1.3Dose Modification

Table 11.1.3.1 No of Patients with Dosing Modifications by Dose Level

No of patients with dosing reduced	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
No				
Yes				
Total				

Table 11.1.3.2 No of Patients with Cycles Reduced by Dose Level

No of patients with cycles reduced	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
No reduction				
1 cycle				
2 cycles				
Total				

Table 11.1.3.3 Reasons for Dose Reduction by Dose Level

No of patients with	Dose level

cycles reduced	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
No dose reduction				
Hematological				
Non-hematological				
Both				
Non-drug related				
Other				
Total				

Table 11.1.3.4 Listing of Dose Reductions

Dose level	Patient No	Cycle	DA Start Date	DA Is infusion reduced?	DA Reduce reason	Specify

11.2 Dose Limiting Toxicities

This analysis will be carried out on the evaluable for RD population.

11.2.1Dose Limiting Toxicities

Table 11.2.1.1 Summary of Patients with DLT by Dose Level

Dose level (mg/m²)	Escalation factor	N	DLT

Note: Each row shows the number of patients N of that Dose Level, the number of cases with defined DLT.

Table 11.2.1.2 Details of DLT

Dose level (mg/m²)	Patient Id	DLT Description	Comments

11.3 Adverse Events (AEs)

This analysis will be carried out on the evaluable for safety population.

11.3.1Display of Adverse Events

Table 11.3.1.1 Drug-Related Adverse Events. Worst Grade by Patient and Dose Level

	Dose level																
	I (N=XX)					… (N=XX)	III (N=XX)					Total (N=XX)					
	Grade																
	1-4	1	2	3	4	…	1-4	1	2	3	4	1-4	1	2	3	4
MedDRA System Organ Class Preferred Term	N (%)	N (%)	N (%)	N (%)	N (%)	…	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Unknown terms included

Table 11.3.1.2 Drug-Related Adverse Events in the First Cycle by Patient and Dose Level

	Dose level																
	I (N=XX)					II (N=XX)	III (N=XX)					Total (N=XX)					
	Grade																
	1-4	1	2	3	4	…	1-4	1	2	3	4	1-4	1	2	3	4
MedDRA System Organ Class Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	…	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

Unknown terms included

Table 11.3.1.3 Drug-Related Adverse Events. Worst Grade Per Cycle by Dose Level

	Dose level															
	I (N=XX)					II (N=XX)	III (N=XX)					Total (N=XX)				
	Grade															
	1-4	1	2	3	4		1-4	1	2	3	4	1-4	1	2	3	4
MedDRA System Organ Class Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	…	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
						…										

Unknown terms included

Table 11.3.1.4 Adverse Events Regardless of Relationship. Worst Grade by Patient by Dose Level

	Dose level															
	I (N=XX)					II (N=XX)	III (N=XX)					Total (N=XX)				
	Grade															
	1-4	1	2	3	4	…	1-4	1	2	3	4	1-4	1	2	3	4
MedDRA System Organ Class Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	…	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

Notes: Percentage is based on number of patients by Dose Level

Table 11.3.1.5 Adverse Events Regardless of Relationship in the First Cycle by Patient and Dose Level

	Dose level															
	I (N=XX)					II (N=XX)	III (N=XX)					Total (N=XX)				
	Grade															
	1-4	1	2	3	4	…	1-4	1	2	3	4	1-4	1	2	3	4
MedDRA System Organ Class Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	…	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

Notes: Percentage is based on number of patients by Dose Level

Table 11.3.1.6 Adverse Events Regardless of Relationship. Worst Grade per Cycle by Dose Level

	Dose level															
	I (N=XX)					II (N=XX)	III (N=XX)					Total (N=XX)				
	Grade															
	1-4	1	2	3	4	…	1-4	1	2	3	4	1-4	1	2	3	4
MedDRA System Organ Class Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	…	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

Notes: Percentage is based on number of patients by Dose Level

Table 11.3.1.7 Adverse Events Observed in ≥10% of Patients regardless of relationship. Worst Grade per Patient by Dose Level

	Dose level															
	I (N=XX)					II (N=XX)	III (N=XX)					Total (N=XX)				
	Grade															
	1-4	1	2	3	4	…	1-4	1	2	3	4	1-4	1	2	3	4
MedDRA System Organ Class Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	…	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

Notes: Percentage is based on number of patients by Dose Level

Table 11.3.1.8 Adverse Events Observed in ≥10% of Patients regardless of relationship. Worst Grade per Cycle by Dose Level

	Dose level															
	I (N=XX)					II (N=XX)	III (N=XX)					Total (N=XX)				
	Grade															
	1-4	1	2	3	4	…	1-4	1	2	3	4	1-4	1	2	3	4
MedDRA System Organ Class Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	…	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

Notes: Percentage is based on number of patients by Dose Level

Table 11.3.1.9 Supportive Listing: Patients with grade >=2 AEs at Baseline

Dose level (mg/m²)	Patient	Lab. test	Examination date	N	Std. value	xULN	Grade CTC v4.0

11.4 Deaths and Other Serious Adverse Events

11.4.1 Deaths

Table 11.4.1.1 Patients who Died While on Treatment

Dose level	Patient No	Last cycle received	Last infusion date	Death date	Time from last infusion date (days)	Cause	Comments	Time on study (weeks)

Note: Patient with Death reported as End of Study Reason.

Table 11.4.1.2 Patients Who Died Within 30 Days of Last Drug Administration

Dose level	Patient No	Last cycle received	Last infusion date	Death date	Time from last infusion date (days)	Cause	Comments	Time on study (weeks)

Table 11.4.1.3 Listing of All Deaths

Dose level	Patient No	Last cycle received	Last infusion date	Death date	Cause	Comments	Autopsy	Time on study (weeks)	Time from last infusion date (days)

Table 11.4.1.4 Summary of All Deaths by Dose Level

Deaths	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Deaths				

11.4.2Serious Adverse Events

Table 11.4.2.1 All SAEs

Dose (mg /m²)	Patient	MedDRA System Organ Class	Preferred Term	Grade	AE Status	AE relationship	AE consequences	SAE	Onset date	Resolved date

Table 11.4.2.2 Drug-Related SAEs. Worst Grade by Patient and Dose Level

	Dose level

	I (N=XX)				… (N=XX)				N (N=XX)				Total (N=XX)			
	Grade															
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
MedDRA System Organ Class Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N (%)

Unknown terms included

Table 11.4.2.3 Drug-Related SAEs in the First Cycle by Patient and Dose Level

	Dose level															
	I (N=XX)				… (N=XX)				N (N=XX)				Total (N=XX)			
	Grade															
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
MedDRA System Organ Class Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

Unknown terms included

Table 11.4.2.4 Drug-Related SAEs. Worst Grade Per Cycle by Dose Level

	Dose level															
	I (N=XX)				II (N=XX)				III (N=XX)				Total (N=XX)			
	Grade															
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
MedDRA System Organ Class Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)

Unknown terms included

Table 11.4.2.5 SAEs Regardless of Relationship. Worst Grade by Patient by Dose Level

	Dose level															
	I (N=XX)				II (N=XX)				III (N=XX)				Total (N=XX)			
	Grade															
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
MedDRA System Organ Class Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N (%)

Notes: Percentage is based on number of patients by Dose Level

Table 11.4.2.6 SAEs Regardless of Relationship in the First Cycle by Patient and Dose Level

	Dose level

	I (N=XX)				II (N=XX)				III (N=XX)				Total (N=XX)			
	Grade															
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
MedDRA System Organ Class Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N (%)

Notes: Percentage is based on number of patients by Dose Level

Table 11.4.2.7 SAEs Regardless of Relationship. Worst Grade per Cycle by Dose Level

	Dose level															
	I (N=XX)				II (N=XX)				III (N=XX)				Total (N=XX)			
	Grade															
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
MedDRA System Organ Class Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N (%)

Notes: Percentage is based on number of patients by Dose Level

Table 11.4.2.8 SAEs Observed in ≥10% of Patients regardless of relationship. Worst Grade per Patient by Dose Level

	Dose level

	I (N=XX)				II (N=XX)				III (N=XX)				Total (N=XX)			
	Grade															
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
MedDRA System Organ Class Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N (%)

Notes: Percentage is based on number of patients by Dose Level

Table 11.4.2.9 SAEs Observed in ≥10% of Patients regardless of relationship. Worst Grade per Cycle by Dose Level

	Dose level															
	I (N=XX)				II (N=XX)				III (N=XX)				Total (N=XX)			
	Grade															
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
MedDRA System Organ Class Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N (%)

Notes: Percentage is based on number of patients by Dose Level

11.5 Clinical Laboratory Evaluation

11.5.1 Hematological Abnormalities

Table 11.5.1.1 Hematological Abnormalities: Worst Grade Per Patient by Dose Level in Cycle 1

Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Anemia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
Leukopenia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
Lymphopenia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
Neutropenia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
XXXXXXX				
Grade 1 - 4, N (%)				

Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Grade 1				
Grade 2				
Grade 3				
Grade 4				

Notes: Percentage is based on number of patients by Dose Level

Table 11.5.1.2 Hematological Abnormalities: Worst Grade Per Cycle by Dose Level in Cycle 1

Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Anemia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
Leukopenia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
Lymphopenia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
Neutropenia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				

Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Grade 4				
XXXXXXX				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				

Notes: Percentage is based on number of patients by Dose Level

Table 11.5.1.3 Hematological Abnormalities: Worst Grade Per Patient by Dose Level

Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Anemia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
Leukopenia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
Lymphopenia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				

Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Neutropenia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
XXXXXXX				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				

Notes: Percentage is based on number of patients by Dose Level

Table 11.5.1.4 Hematological Abnormalities: Worst Grade Per Cycle by Dose Level

Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Anemia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				

Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Leukopenia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
Lymphopenia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
Neutropenia				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
XXXXXXX				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				

Notes: Percentage is based on number of patients by Dose Level

Table 11.5.1.5 Supportive Listing: Patients with Grade ≥3 Hematological Abnormalities.

Dose level (mg/m²)	Patient	Lab. test	Cycle	Examination date	N	Std. value	Normal Range	Grade CTC v4.0

Dose level (mg/m²)	Patient	Lab. test	Cycle	Examination date	N	Std. value	Normal Range	Grade CTC v4.0

Table 11.5.1.6 Supportive Listing: Patients with grade >=2 Hematological Abnormalities at Baseline

Dose level (mg/m²)	Patient	Lab. test	Examination date	N	Std. value	xULN	Grade CTC v4.0

11.5.2Biochemical Abnormalities

Table 11.5.2.1 Biochemical Abnormalities: Worst Grade Per Patient by Dose Level in Cycle 1

Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
AP increase				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
ALT increase				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				

Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Grade 4				
AST increase				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
Amylase increased				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
XXXXXXX				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				

Notes: Percentage is based on number of patients by Dose Level

Table 11.5.2.2 Biochemical Abnormalities: Worst Grade Per Cycle by Dose Level in Cycle 1

Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
AP increase				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				

Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
ALT increase				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
AST increase				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
Amylase increased				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
XXXXXXX				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				

Notes: Percentage is based on number of patients by Dose Level

Table 11.5.2.3 Biochemical Abnormalities: Worst Grade Per Patient by Dose Level

Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
AP increase				
Grade 1 - 4, N (%)				

Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Grade 1				
Grade 2				
Grade 3				
Grade 4				
ALT increase				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
AST increase				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
Amylase increased				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
XXXXXXX				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				

Notes: Percentage is based on number of patients by Dose Level

Table 11.5.2.4 Biochemical Abnormalities: Worst Grade Per Cycle by Dose Level

Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
AP increase				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
ALT increase				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
AST increase				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
Amylase increased				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				
XXXXXXX				
Grade 1 - 4, N (%)				
Grade 1				
Grade 2				
Grade 3				
Grade 4				

Notes: Percentage is based on number of patients by Dose Level

Table 11.5.2.5 Supportive Listing: Patients with ~~Some~~ Grade ≥3 Biochemical Abnormalities.

Dose level (mg/m²)	Patient	Lab. test	Cycle	Examination date	N	Std. value	Value (xULN)	Grade CTC v4.0

Table 11.5.2.6 Supportive Listing: Patients with grade >=2 Biochemical Abnormalities at Baseline

Dose level (mg/m²)	Patient	Lab. test	Examination date	N	Std. value	xULN	Grade CTC v4.0

11.5.3Laboratory Values over Time

Table 11.5.3.1 Worst Severity of Hematological Abnormalities During the First and Later Cycles by Dose Level

Over time	Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Cycle 1	Anemia/…				
	Grade 1-4, N (%)				
	Grade 1				
	Grade 2				
	Grade 3				
	Grade 4				

Over time	Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Cycle>1	Anemia/…				
	Grade 1-4, N(%)				
	Grade 1				
	Grade 2				
	Grade 3				
	Grade 4				

Notes: Percentage is based on number of patients by Dose Level

Table 11.5.3.2 Worst Severity of Biochemical Abnormalities During the First and Later Cycles by Dose Level

Over time	Toxicity	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Cycle 1	AP increase/…				
	Grade 1-4, N(%)				
	Grade 1				
	Grade 2				
	Grade 3				
	Grade 4				
Cycle>1	AP increase/…				
	Grade 1-4, N(%)				
	Grade 1				
	Grade 2				
	Grade 3				
	Grade 4				

Notes: Percentage is based on number of patients by Dose Level

11.6 Vital Signs

11.6.1 Vital Signs, Physical Findings and Other Observations Related to Safety

Table 11.6.1.1 Physical Examination during treatment by Dose Level

Physical Examination	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Normal				
Abnormal				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 11.6.1.2 Supportive Listing: Physical Examination Abnormal

Patient No	Date of physical exam	Weight	Body surface area

Table 11.6.1.3 Electrocardiogram Measures during treatment.

Dose level	Patient	Cycle	PR interval	RR interval	…	Max height of QRS complex

Table 11.6.1.4 Electrocardiogram Results during treatment by Dose Level .

Electrocardiogram Results	Dose level						
	I (N=XX)	II (N=XX)	III (N=XX)	… (N=XX)	… (N=XX)	N (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Normal							
Significant Abnormalities							
Non-significant Abnormalities							
Total							

Table 11.6.1.5 Supportive Listing: Electrocardiogram Abnormalities during treatment

Dose level	Patient No	Abnormality Specification

Table 11.6.1.6 Left Ventricular Ejection Fraction (LVEF) during treatment

LVEF	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Normal				
Significant Abnormalities				
Non-significant Abnormalities				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 11.6.1.7 Mean, Median, Std and Range values of Left Ventricular Ejection Fraction (LVEF) during treatment (MUGA)

MUGA	Dose level

	I (N=XX) N(%)	II (N=XX) N(%)	III (N=XX) N(%)	Total (N=XX) N(%)
Mean				
Median				
Std				
Minimum				
Maximum				

Notes: Percentage is based on number of patients by Dose Level

Table 11.6.1.8 Mean, Median, Std and Range values of Left Ventricular Ejection Fraction (LVEF) during treatment (ECHO)

ECHO	Dose level			
	I (N=XX) N(%)	II (N=XX) N(%)	III (N=XX) N(%)	Total (N=XX) N(%)
Mean				
Median				
Std				
Minimum				
Maximum				

Notes: Percentage is based on number of patients by Dose Level

Table 11.6.1.9 Performance Status During the Study by Cycle and Dose Level

Cycle

		Baseline	Cycle 1	Cycle 2	Total
Dose level	Patient No	Performance status	Performance status	Performance status	Performance status
I (N=XX)					
II (N=XX)					
III (N=XX)					
Total (N=XX)					

If more than one measurement, only worst will be presented

Table 11.6.1.10 Weight Gain-Loss During the Study by Dose Level

			Cycle			
			Baseline	Cycle 1	Cycle 2	Total
Dose level	Patient No	Weight at baseline (kg)	% change	% change	% change	% change
I (N=XX)						
II (N=XX)						

			Cycle			
			Baseline	Cycle 1	Cycle 2	Total
Dose level	Patient No	Weight at baseline (kg)	% change	% change	% change	% change
III (N=XX)						
Total (N = XX)						

If more than one measurement, only worst will be presented

Table 11.6.1.2 Troponin Values. Evolution During Study

Dose level	Patient	Cycle	Troponin I Value	Troponin T Value	ULN
	…				
	…				
	…				

11.7 Concomitant Medication

11.7.1 Concomitant Medication During Study

Table 11.7.1.1 Concomitant Medication During Study (ATC Level 1, 2 and 4) by Dose Level

Medication Term (ATC level 1)	Medication Term (ATC level 2)	Medication Term (ATC level 4)	Dose level			
			I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
			N(%)	N(%)	N(%)	N(%)

Notes: Percentage is based on number of patients by Dose Level

Table 11.7.1.2 Transfusions

Type	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Platelet transfusion				
RBC transfusion				
…				

Notes: Percentage is based on number of patients by Dose Level

12 Appendix III. Efficacy Evaluation

This analysis will be carried out on the evaluable for efficacy population.

12.1 Efficacy Analysis

12.1.1 Response

Table 12.1.1.1 Overall Response Rate

Summary
Estimate proportion
95% Confidence Interval (XX – XX)*

(*) Calculated using exact binomial distribution.

Table 12.1.1.2 Overall response by Dose Level. Treated Patients

Overall response	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Response Criteria for Multiple Myeloma				
sCR				
CR				
VGPR				
PR				
MR				
SD < 4 months				
SD ≥ 4 months				
PD				

Overall response	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
NE				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 12.1.1.3 SD ≥ 4 months by Dose Level. Treated Patients

SD≥4 months	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
No				
Yes				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 12.1.1.4 Overall response by Dose Level. Evaluable Population

Overall response	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Response Criteria for Multiple Myeloma				
sCR				
CR				
VGPR				

Overall response	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
PR				
MR				
SD<4 months				
SD≥4 months				
PD				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 12.1.1.5 SD ≥ 4 months by Dose Level. Evaluable population

SD≥4 months	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
No				
Yes				
Total				

Notes: Percentage is based on number of patients by Dose Level

Table 12.1.1.6 Clinical Benefit Rate*

Summary
Estimate proportion*
95% Confidence Interval (XX – XX)**

(*)Let define 'Evidence of Clinical Benefit' when response is sCR, CR, VGPR, PR, MR or SD
(**) Calculated using exact binomial distribution.

Table 12.1.1.6B Clinical Benefit Rate*

Summary
Estimate proportion*
95% Confidence Interval (XX – XX)**

(*)(*)Let define 'Evidence of Clinical Benefit' when response is sCR, CR, VGPR, PR, MR

(**) Calculated using exact binomial distribution.

Table 12.1.1.7 Characteristics of Patients with Evidence of Clinical Benefit*

Patient No	Dose Level	Sex	Age	PS	MM type	Relapse / Refractory-Relapse / Refractory	Number of lines of previous treatment	ASCT**	Agents (previous treatment)	Best Response last Previous CT	TTP last CT	Cycles Received	Overall Response	PFS (months)	Overall Survival (months)	Treatment Discontinuation Reason	Cause of death

(*) Let define "Evidence of Clinical Benefit" when response is sCR, CR, VGPR, PR, MR or SD
(**) Autologous Stem Cell Transplantation

Table 12.1.1.8 Supportive Listing Efficacy Dataset Analyzed

Dose level	Patient	Evaluable	Evaluation criteria	Best Response	Progression	Progression Date	Death	Death Date

Table 12.1.1.9 Progression-Free Survival Treated Population

Summary
N=XX
Events X (XX.X%)
Censored X (XX.X%)
Median X.X 95% CI (XX-XX)
PFS at 3 months XX.X% 95% CI (XX-XX)
PFS at 6 months XX.X% 95% CI (.XX-XX)

Table 12.1.1.10 Progression-Free Survival Evaluable Population

Summary
N=XX
Events X (XX.X%)
Censored X (XX.X%)
Median X.X 95% CI (XX-XX)
PFS at 3 months XX.X% 95% CI (XX-XX)
PFS at 6 months XX.X% 95% CI (.XX-XX)

Table 12.1.1.11 Overall Survival. Treated Population

Summary
N=XX
Events X (XX%)
Censored X (XX%)
Median X.X 95% CI (X.X-X.X)
OS at 6 months XX.X% 95% CI (XX.-XX)
OS at 12 months XX.X% 95% CI (XX-XX)

Table 12.1.1.12 Overall Survival. Evaluable Population

Summary
N=XX
Events X (XX%)
Censored X (XX%)
Median X.X 95% CI (X.X-X.X)
OS at 6 months XX.X% 95% CI (XX.-XX)
OS at 12 months XX.X% 95% CI (XX-XX)

Table 12.1.1.13 Duration of Response. Treated Population

Summary
N=XX

Summary
Events X (XX%)
Censored X (XX%)
Median X.X 95% CI (X.X-X.X)
Duration of Response at 3 months XX.X% 95% CI (XX.-XX)
Duration of Response at 6 months XX.X% 95% CI (XX-XX)

Table 12.1.1.14 Duration of Response. Evaluable Population

Summary
N=XX
Events X (XX%)
Censored X (XX%)
Median X.X 95% CI (X.X-X.X)
Duration of Response at 3 months XX.X% 95% CI (XX.-XX)
Duration of Response at 6 months XX.X% 95% CI (XX-XX)

Table 12.1.1.15 Time-To-Progression. Treated Population

Summary
N=XX
Events X (XX%)
Censored X (XX%)
Median X.X 95% CI (XX-XX)
PFS at 3 months XX.X% 95% CI (XX-XX)
PFS at 6 months XX.X% 95% CI (.XX-XX)

Table 12.1.1.16 Time-To-Progression. Evaluable Population

Summary
N=XX
Events X (XX%)
Censored X (XX%)
Median X.X 95% CI (XX-XX)
PFS at 3 months XX.X% 95% CI (XX-XX)
PFS at 6 months XX.X% 95% CI (.XX-XX)

Table 12.1.1.17 Event-Free Survival. Treated Population

Summary
N=XX
Events X (XX%)
Censored X (XX%)
Median X.X 95% CI (XX-XX)
PFS at 3 months XX.X% 95% CI (XX-XX)
PFS at 6 months XX.X% 95% CI (.XX-XX)

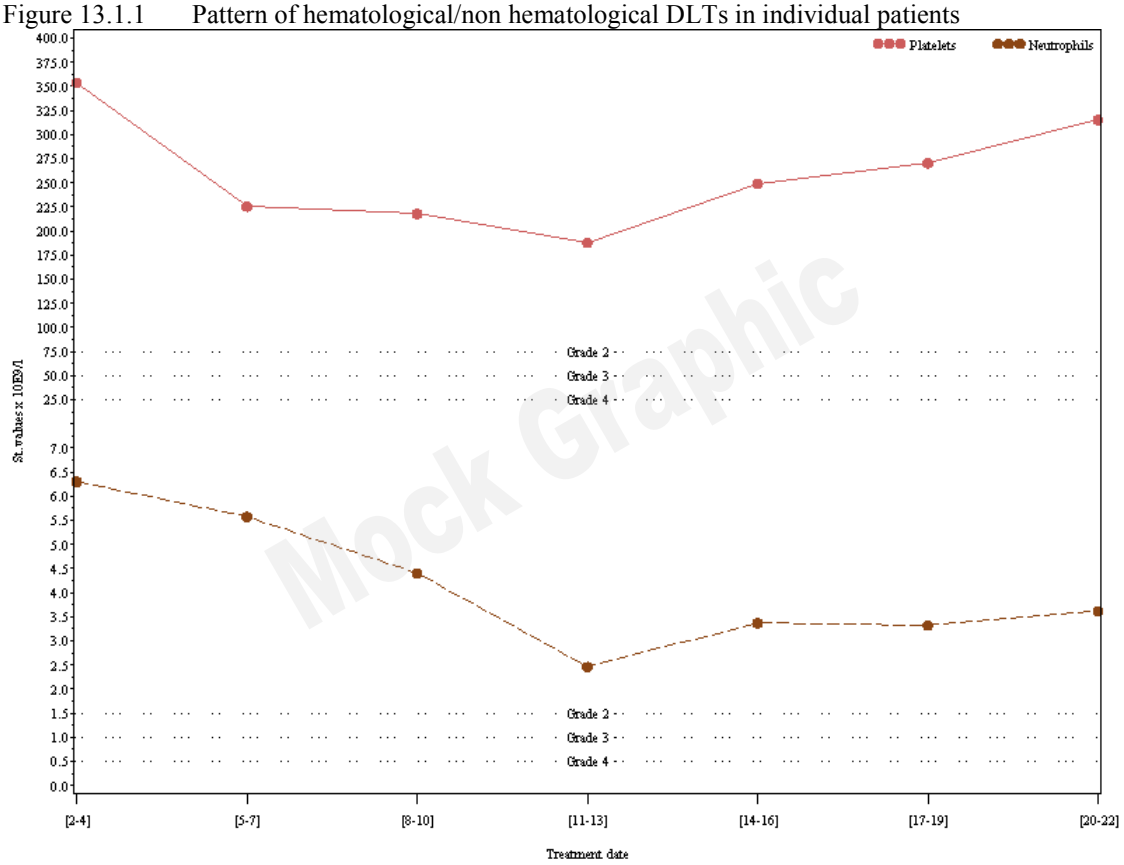
Table 12.1.1.18 Event-Free Survival. Evaluable Population

Summary
N=XX
Events X (XX%)
Censored X (XX%)
Median X.X 95% CI (XX-XX)
PFS at 3 months XX.X% 95% CI (XX-XX)
PFS at 6 months XX.X% 95% CI (.XX-XX)

13 Figures

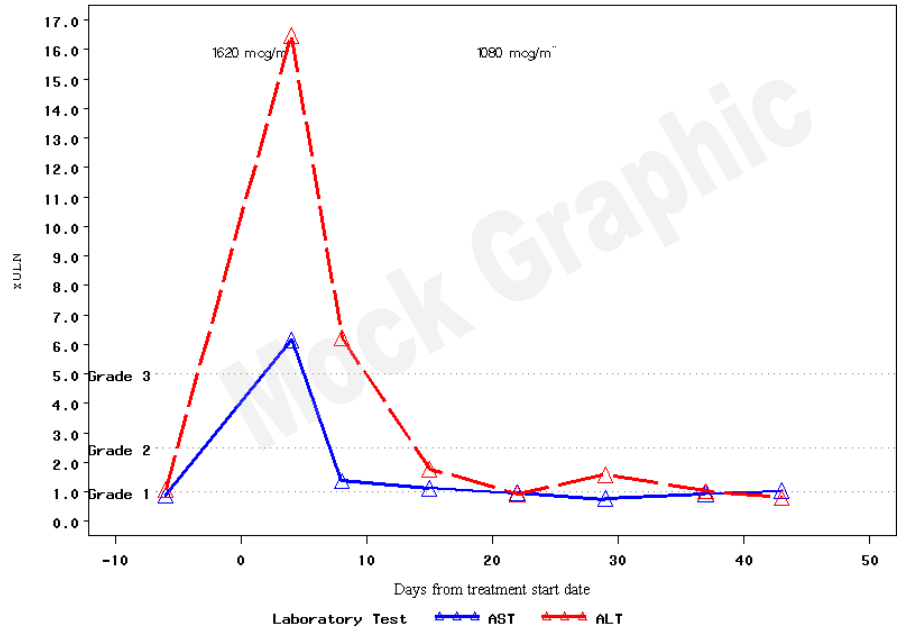
13.1 Hematological Profile

Figure 13.1.1 Pattern of hematological/non hematological DLTs in individual patients



13.2 Transaminase Profile

Figure 13.2.1 Transaminase series. Patient XX



This profile will be done to patients with DLTs related to Transaminase

Figure 13.2.2 Bar charts of hematological/biochemical laboratory abnormalities by dose level

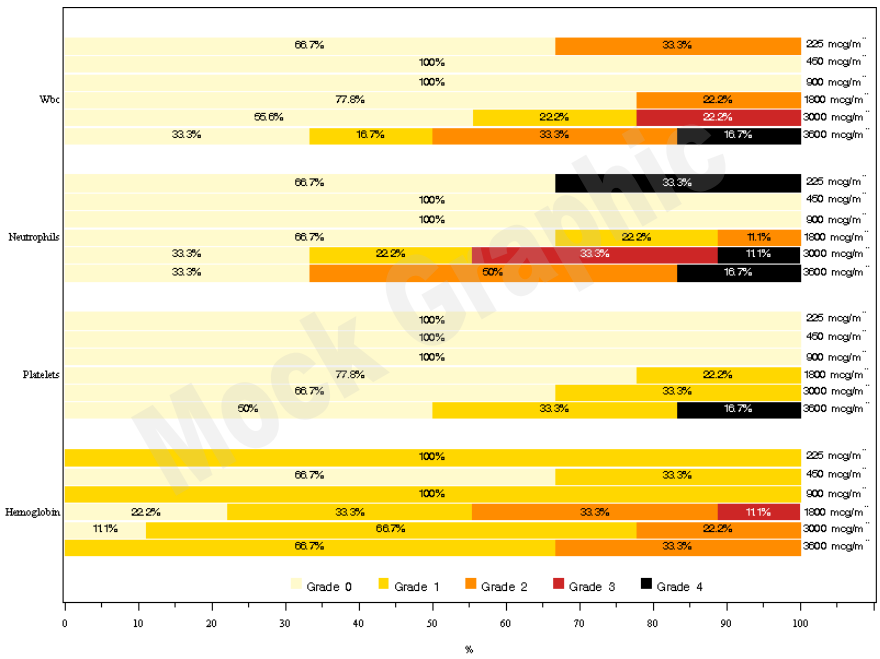
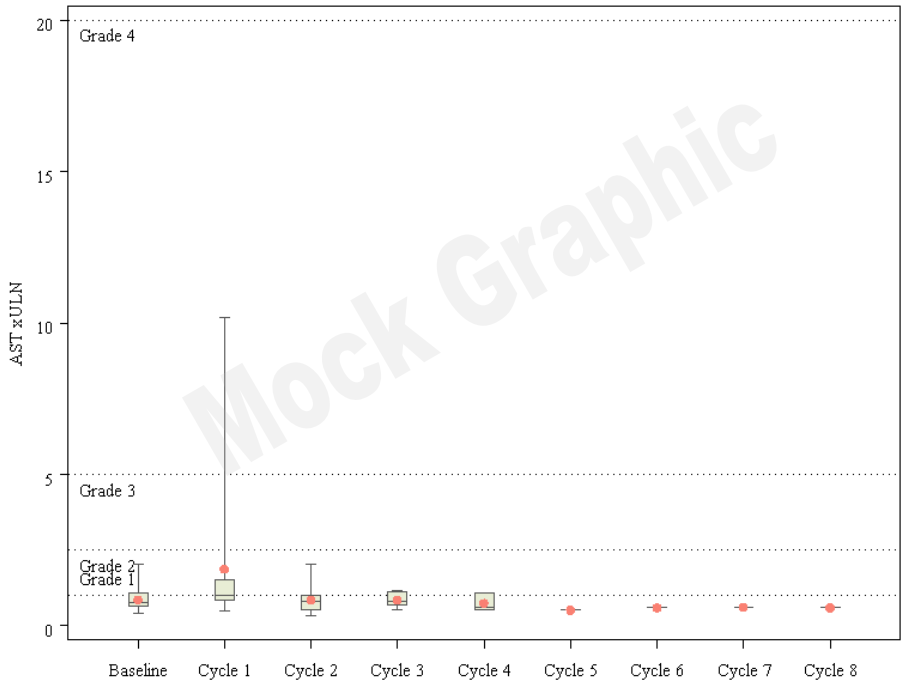
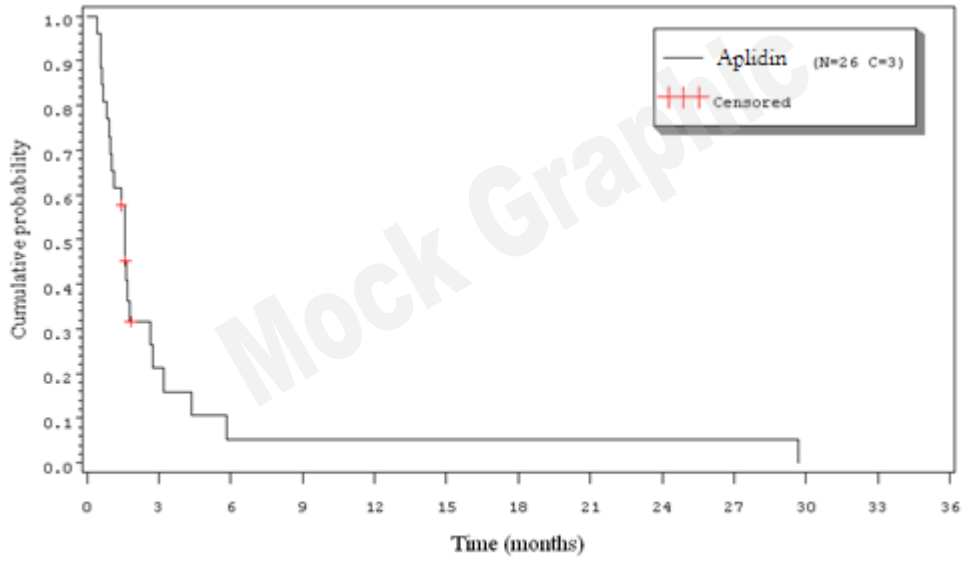


Figure 13.2.3 Hematology / Transaminase Worst Severity by Cycle



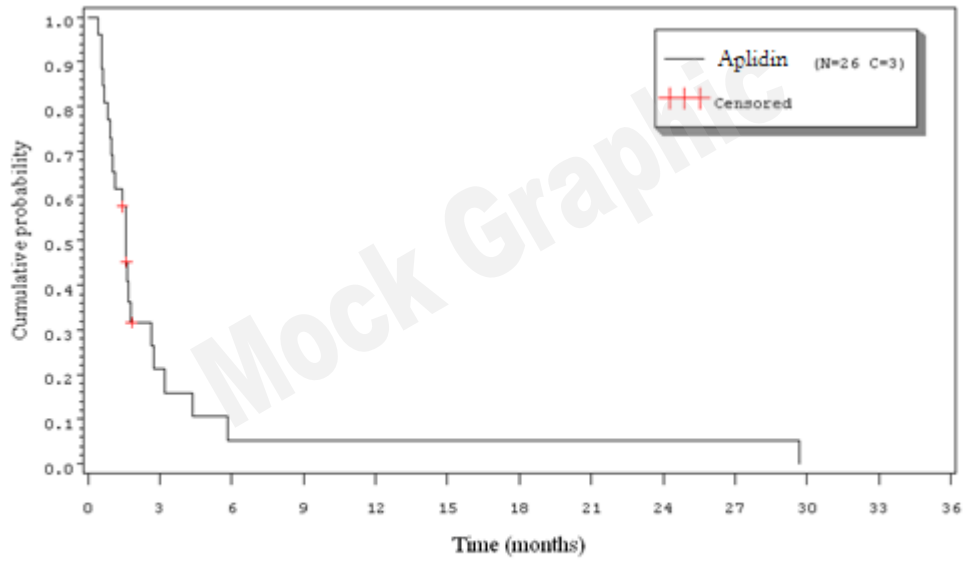
13.3 Time to Event Graphs

Figure 13.3.1 Progression-Free Survival (PFS)



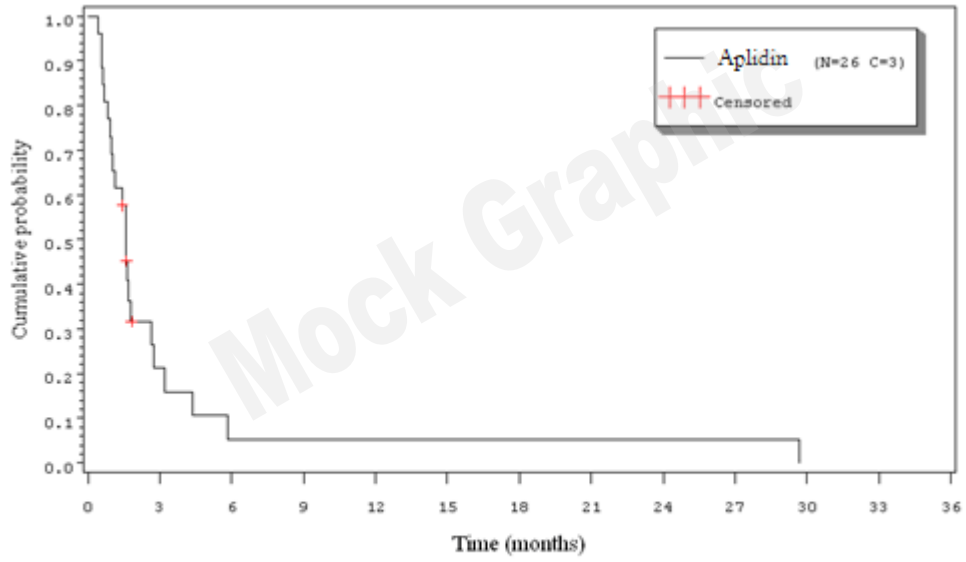
Median 1.6 95% CI (1.0-2.7)
PFS at 3 months 21.2% 95% CI (3.9%-38.4%)
PFS at 6 months 5.3% 95% CI (0%-15.3%)
PFS at 12 months 5.3% 95% CI (0%-15.3%)

Figure 13.3.2 Overall Survival (OS)



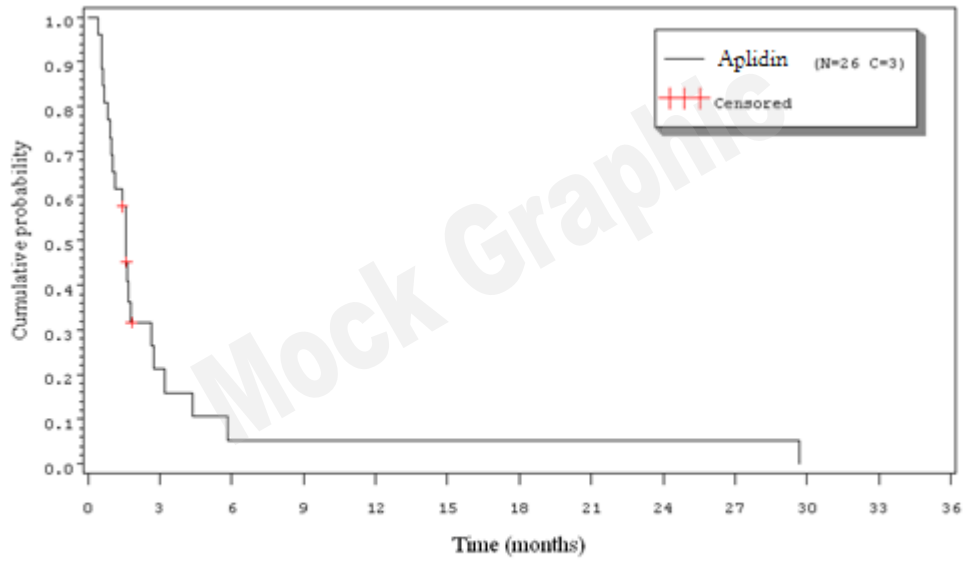
Median 1.6 95% CI (1.0-2.7)
PFS at 3 months 21.2% 95% CI (3.9%-38.4%)
PFS at 6 months 5.3% 95% CI (0%-15.3%)
PFS at 12 months 5.3% 95% CI (0%-15.3%)

Figure 13.3.3 Duration of response (DOR)



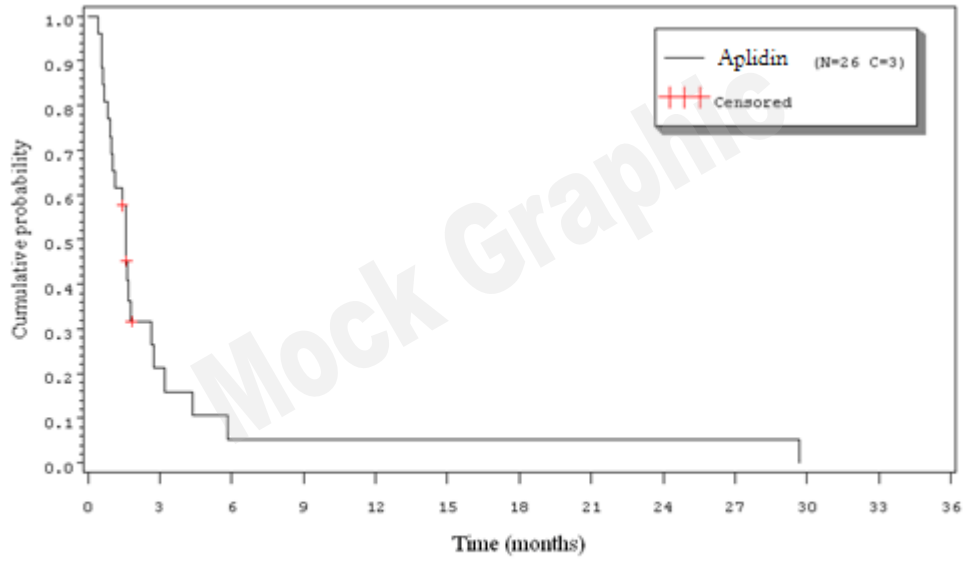
Median 1.6 95% CI (1.0-2.7)
PFS at 3 months 21.2% 95% CI (3.9%-38.4%)
PFS at 6 months 5.3% 95% CI (0%-15.3%)
PFS at 12 months 5.3% 95% CI (0%-15.3%)

Figure 13.3.4 Time to Progression (TTP)



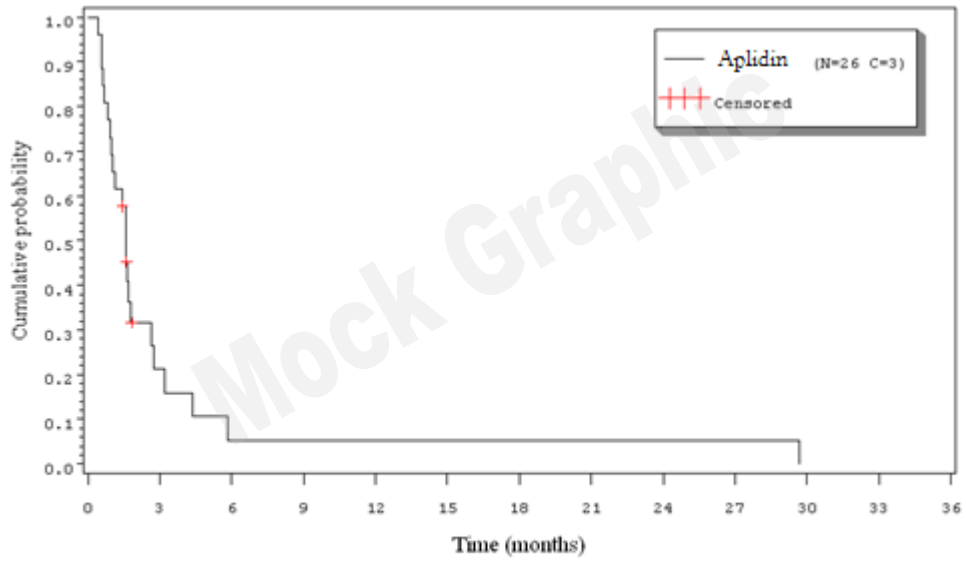
Median 1.6 95% CI (1.0-2.7)
PFS at 3 months 21.2% 95% CI (3.9%-38.4%)
PFS at 6 months 5.3% 95% CI (0%-15.3%)
PFS at 12 months 5.3% 95% CI (0%-15.3%)

Figure 13.3.5 Event Free Survival (EFS)



Median 1.6 95% CI (1.0-2.7)
PFS at 3 months 21.2% 95% CI (3.9%-38.4%)
PFS at 6 months 5.3% 95% CI (0%-15.3%)
PFS at 12 months 5.3% 95% CI (0%-15.3%)

Figure 13.3.6 Time to Onset (TTO)



Median 1.6 95% CI (1.0-2.7)
PFS at 3 months 21.2% 95% CI (3.9%-38.4%)
PFS at 6 months 5.3% 95% CI (0%-15.3%)
PFS at 12 months 5.3% 95% CI (0%-15.3%)

Figure 13.3.7 Example of plot of individual m-protein values of responder patients.

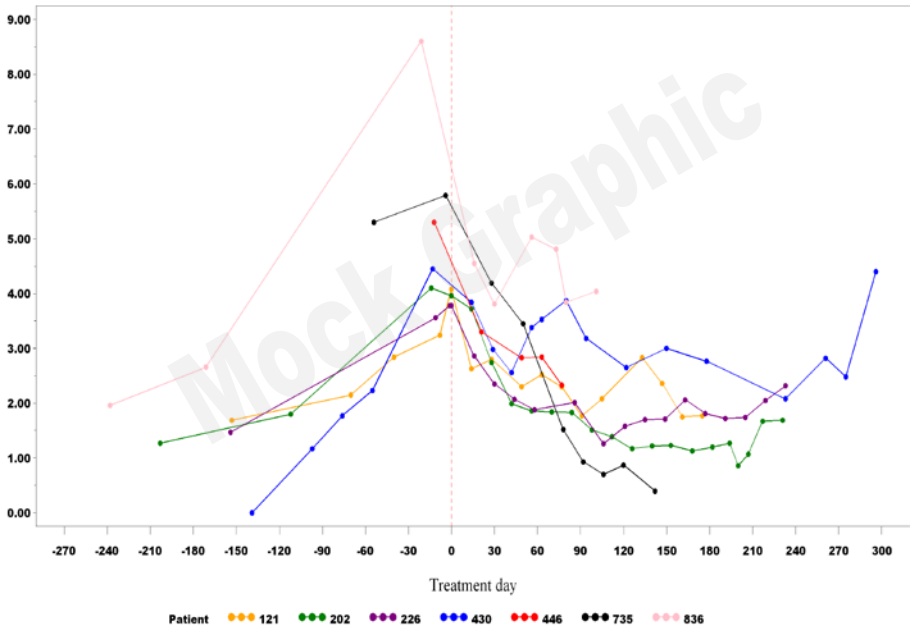


Figure 13.3.8 Waterfall plot. (Maximum reduction of m-protein in serum)

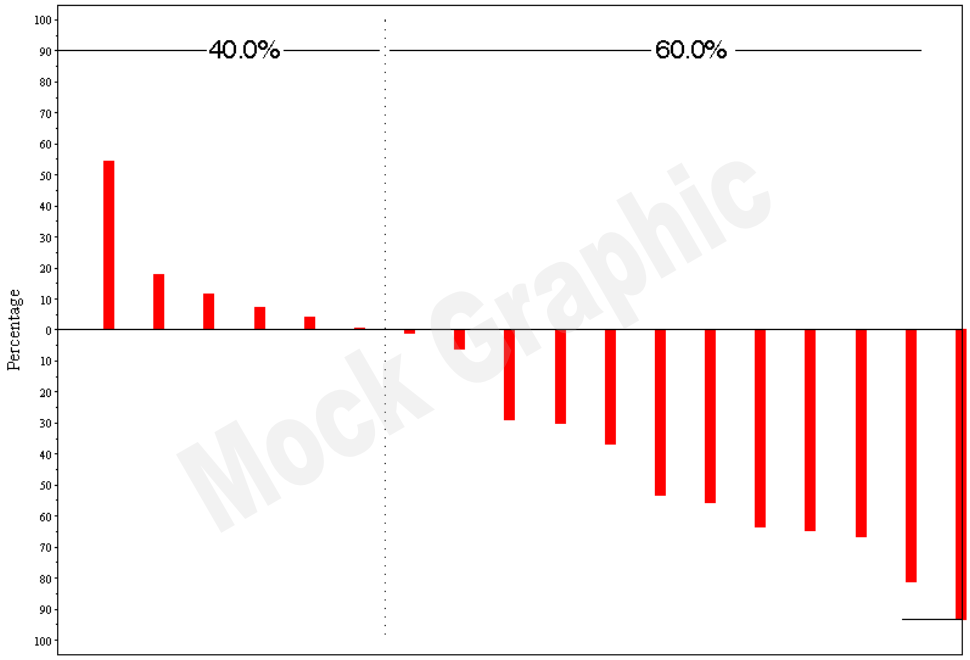
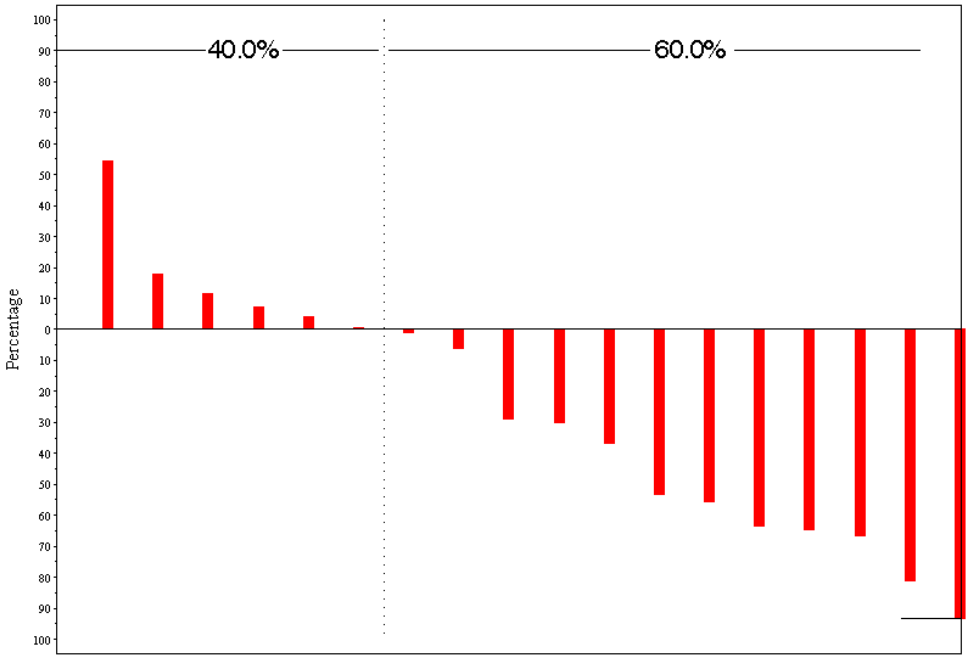


Figure 13.3.9 Waterfall plot. (Maximum reduction of m-protein in urine)



14 DB Listing

-Listing 14.1.1: Study registration
-Listing 14.1.2: Demography
-Listing 14.1.3: Medical history
-Listing 14.1.4: Pregnancy test
-Listing 14.1.5: MM history
-Listing 14.1.6: End of Treatment
-Listing 14.1.7: Adverse Events
-Listing 14.1.8: SAE Summary
-Listing 14.1.9: Concomitant Therapy/Procedures
-Listing 14.1.10: Blood products use
-Listing 14.1.11: Prior AntiCancer Therapy: Palliative RadioTherapy
-Listing 14.1.12: Prior AntiCancer Medical Therapy for Study Disease
-Listing 14.1.13: Unscheduled
-Listing 14.1.14: Hematology
-Listing 14.1.15: Coagulation Test
-Listing 14.1.16: Biochemistry A
-Listing 14.1.17: Biochemistry B
-Listing 14.1.18: Physical Examination
-Listing 14.1.19: Clinical Neurological Assessment
-Listing 14.1.20: Performance Status
-Listing 14.1.21: Vital Signs
-Listing 14.1.22: Electrocardiogram (also after Plitidepsin admin.)
-Listing 14.1.23: Left Ventricular Ejection Fraction (LVEF)
-Listing 14.1.24: Viral Serology
-Listing 14.1.25: Follow Up
-Listing 14.1.26: Surgery Procedures for Study Disease (after End of Treatment)
-Listing 14.1.27: Radiotherapy (after End of Treatment)
-Listing 14.1.28: Medical Treatment (after End of Treatment)
-Listing 14.1.29: MM Serum Protein Measurements
-Listing 14.1.30: MM Urine Protein Measurements
- Listing 14.1.31: C-Reactive Protein
-Listing 14.1.32: Beta-2-microglobulin
-Listing 14.1.33: Tumor Evaluation
-Listing 14.1.34: Skeletal Evaluation
-Listing 14.1.35: Bone Marrow Evaluation
-Listing 14.1.36: Evaluation of Response
-Listing 14.1.37: Prophylactic Mediation (Per Protocol)
-Listing 14.1.38: Oral Dexamethasone Administration
-Listing 14.1.39: Plitidepsin Administration
-Listing 14.1.40: Plitidepsion Readministration

-Listing 14.1.41: Bortezomib Administration
-Listing 14.1.42: Urinalysis
-Listing 14.1.43: Other test/Procedures
-Listing 14.1.44: Best Overall Response / Off Study
-Listing 14.1.45: Death Resport Form

15 SAP Version History

Two substancial protocol amendments (Number 1 on 23SEP2015 and number 2 on 08OCT2015) have been implemented after the first version of the statistical analysis plan (SAP) was approved. The SAP has been updated accordingly.

The most relevant changes to the SAP are:

-Patient evaluability criteria for the efficacy analysis have been updated to include the need for patients to have undergone at least one disease assessment in order to be considered evaluable.

-Clinical Benefit Rate defined as sCR, CR, VGPR, PR and MR has been added to the previous one defined in the protocol as sCR, CR, VGPR, PR, MR and SD.

-Some tables have been renumbered

-Some tables have been deleted because after physician consultation they are not enough informative to be shown.

-Other minor corrections have also been made, e.g. a reference has been added to the protocol.

Summary of proposed changes

Changes are highlighted in ***Italic bold***. Text removed has been crossed out (~~crossed out~~).

Section 6.4 Population Evaluable for Efficacy

Original text:

Although it is not the main objective of this study, antitumor activity will be measured clinically and/or radiologically according to IMWG. Patients will be evaluable for

efficacy if they meet all inclusion criteria and no exclusion criteria and receive at least one complete treatment cycle (two plitidepsin infusions, four bortezomib injections, four doses of dexamethasone) without protocol deviations with an effect on the risk/benefit ratio of the clinical trial, which may jeopardize the efficacy evaluation. Patients from this population who have inadequate post-baseline data to assess efficacy according to the response criteria (see section 6.1.1 of the protocol) will be considered treatment failures and will be included in the ORR and clinical benefit calculations.

Changes to:

Although it is not the main objective of this study, antitumor activity will be measured clinically and/or radiologically according to IMWG. Patients will be evaluable for efficacy if they meet all inclusion criteria and no exclusion criteria and ***receive at least one treatment cycle*** (two plitidepsin infusions, four bortezomib injections, four doses of dexamethasone) ***and have at least one disease assessment*** without protocol deviations with an effect on the risk/benefit ratio of the clinical trial, which may jeopardize the efficacy evaluation. Patients from this population who have inadequate post-baseline data to assess efficacy according to the response criteria (see section 6.1.1 of the protocol) will be considered treatment failures and will be included in the ORR and clinical benefit calculations.

Section 8.4.1 Exploratory Analysis of Antitumor Activity

Original text:

Patients from this population who have inadequate post-baseline data to assess efficacy according to the response criteria in Section **¡Error! No se encuentra el origen de la referencia.** of the protocol will be considered treatment failures and will be included in the ORR and clinical benefit calculations

Changes to:

Patients from this population who have inadequate post-baseline data to assess efficacy according to the response criteria in Section ~~¡Error! No se encuentra el origen de la referencia~~ ***6.1.1*** of the protocol will be considered treatment failures and will be included in the ORR and clinical benefit calculations

Section 10.2.2 Multiple Myeloma History

Some tables have been renamed because of typing mistakes:

Table 10.2.2.2 Multiple Myeloma Type by Dose Level renamed to ***Table 10.2.2.3 Multiple Myeloma Type by Dose Level***

Table 10.2.2.3 Durie-Salmon stage at First Diagnosis by Dose Level renamed *to* ***Table 10.2.2.4 Durie-Salmon Stage at First Diagnosis by Dose Level***

Table 10.2.2.4 Durie-Salmon Sub-classification at First Diagnosis by Dose Level renamed to ***Table 10.2.2.5 Durie-Salmon Sub-classification at First Diagnosis by Dose Level***

Table 10.2.2.5 ISS stage at First Diagnosis by Dose Level renamed to ***Table 10.2.2.6 ISS stage at First Diagnosis by Dose Level***

Table 10.2.2.6 ISS stage at First Diagnosis by Dose Level renamed to ***Table 10.2.2.7 ISS stage at First Diagnosis by Dose Level***

Section 11.1.1 Cumulative Dose, Dose Intensity and Relative Dose Intensity

In Table 11.1.1.1: the column 'No of patients (Accumulated)' has been deleted:

Table 11.1.1.2 No of cycles administered

		Patients	
Dose level	Max cycle infused	No of patients	~~No of patients (Accumulated)~~
I	Cycle 1 Cycle 2		
II	Cycle 1 Cycle 2		
III	Cycle 1 Cycle 2		
…	Cycle 1 Cycle 2		
N	Cycle 1 Cycle 2		
Total	Cycle 1 Cycle 2 Cycle 3 … Cycle N		

In Table 11.1.2.3 the cell named 'Nº cycles with' has been corrected.

Original table:

Table 11.1.2.4 Number of Cycles with Drug Related Delay per patient by Dose Level

~~No cycles with~~ :	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
No cycle delayed				
01 cycle delayed				
02 cycles delayed				
…				
…				
Total				
Mean				
Median				
Std				
Min				
Max				

Changes to:

Table 11.1.2.5 Number of Cycles with Drug Related Delay per patient by Dose Level

No. of patients with:	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
No cycle delayed				
01 cycle delayed				
02 cycles delayed				
…				
…				
Total				
Mean				
Median				
Std				
Min				
Max				

Section 11.6.1 Vital Signs, Physical Findings and Other Observations Related to Safety

Three tables have been deleted because it is meaningless to analyze the weight, height and BSA during the treatment (as these tables were displayed). And the following tables have been renamed according with this change.

Deleted:

Table 11.6.1.1 Weight during treatment by Dose Level

Weight (Kg)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Median				
Mean				
Std				
Min				
Max				

Table 11.6.1.2 Height during treatment by Dose Level

Height (cm)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				
Median				
Mean				
Std				
Min				
Max				

Table 11.6.1.3 Body Surface Area (BSA) during treatment by Dose Level

BSA (m^2)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
N				

BSA (m^2)	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
Median				
Mean				
Std				
Min				
Max				

Renamed:

Table 11.6.1.4 Supportive Listing: Physical Examination Abnormal renamed to ***Table 11.6.1.2 Supportive Listing: Physical Examination Abnormal***

Table 11.6.1.5 Electrocardiogram Measures during treatment renamed to ***Table 11.6.1.3 Electrocardiogram Measures during treatment***

Table 11.6.1.6 Electrocardiogram Results during treatment by Dose Level renamed to ***Table 11.6.1.4 Electrocardiogram Results during treatment by Dose Level***

Table 11.6.1.7 Supportive Listing: Electrocardiogram Abnormalities during treatment renamed to ***Table 11.6.1.5 Supportive Listing: Electrocardiogram Abnormalities during treatment***

Table 11.6.1.8 Left Ventricular Ejection Fraction (LVEF) during treatment renamed to ***Table 11.6.1.6 Supportive Listing: Electrocardiogram Abnormalities during Treatment***

Table 11.6.1.9 Mean, Median, Std and Range values of Left Ventricular Ejection Fraction (LVEF) during treatment (MUGA) renamed to ***Table 11.6.1.7 Mean, Median, Std and Range values of Left Ventricular Ejection Fraction (LVEF) during treatment (MUGA)***

Table 11.6.1.10 Mean, Median, Std and Range values of Left Ventricular Ejection Fraction (LVEF) during treatment (ECHO) renamed to ***Table 11.6.1.8 Mean, Median, Std and Range values of Left Ventricular Ejection Fraction (LVEF) during treatment (ECHO)***

Table 11.6.1.11 Performance Status During the Study by Cycle and Dose Level renamed to ***Table 11.6.1.9 Performance Status During the Study by Cycle and Dose Level***

Table 11.6.1.12 Weight Gain-Loss During the Study by Dose Level renamed to Table ***11.6.1.13 Weight Gain-Loss During the Study by Dose Level***

In Table 11.6.1.5: the column ***'Height' has been deleted*** because this parameter is not recorded in the physical examination during treatment

Original table:

Table 11.6.1.5 Supportive Listing: Physical Examination Abnormal

Patient No	Date of physical exam	Weight	~~Height~~	Body surface area

Changes to:

Table 11.6.1.2 Supportive Listing: Physical Examination Abnormal

Patient No	Date of physical exam	Weight	Body surface area

Section 11.7.1. Concomitant Medication During Study

Original table:

Table 11.7.1.1 Transfusions

~~Medication Term (ATC level 1)~~	~~Medication Term (ATC level 4)~~	Dose level			
		I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
		N(%)	N(%)	N(%)	N(%)
Platelet transfusion					
RBC transfusion					
…					

Notes: Percentage is based on number of patients by Dose Level

Changes to:

Table 11.7.1.2 Transfusions

Type	Dose level			
	I (N=XX)	II (N=XX)	III (N=XX)	Total (N=XX)
	N(%)	N(%)	N(%)	N(%)
Platelet transfusion				
RBC transfusion				
…				

Notes: Percentage is based on number of patients by Dose Level

Section 12.1.1 Response

Added:

Table 12.1.1.6B Clinical Benefit Rate*

Summary
Estimate proportion*
95% Confidence Interval (XX – XX)**

(*)Let define 'Evidence of Clinical Benefit' when response is sCR, CR, VGPR, PR, MR
(**) Calculated using exact binomial distribution.

SECTION 13.

In Figure 13.3.3 the legend has been deleted and the new word 'serum' has been added to the title:

Figure 13.3.4 Waterfall plot. (Maximum reduction of m-protein) renamed to Figure 13.3.5 Waterfall plot. (Maximum reduction of m-protein **in serum)**

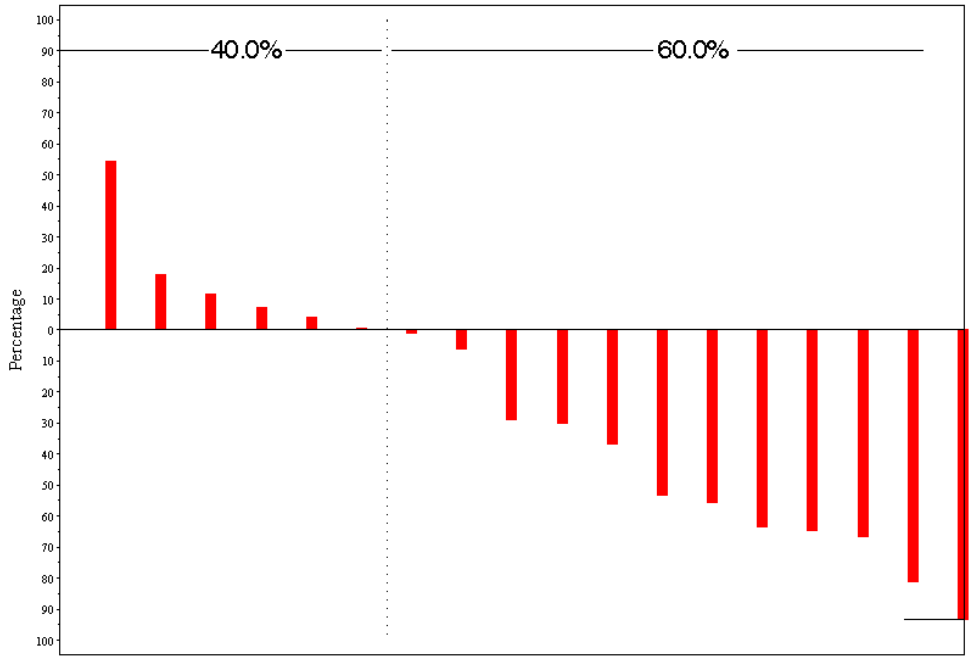
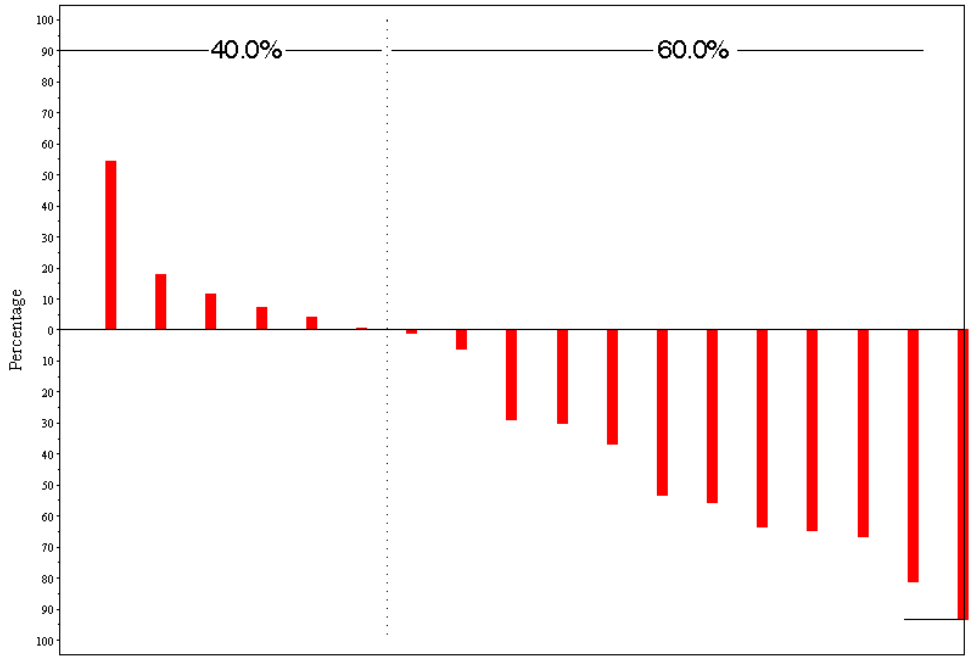


Figure added:

Figure 13.3.9 Waterfall plot. (Maximum reduction of m-protein in urine)



As the company has changed its logo, the SAP has been updated accordingly:

Original logo:

Changes to: